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# JOURNAL

## U.S. ARMY MEDICAL DEPARTMENT

*October-December 2004*

**USAMRMC**  
**UNITED STATES ARMY MEDICAL RESEARCH**  
**AND MATERIEL COMMAND**



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# JOURNAL

U.S. ARMY MEDICAL DEPARTMENT

*A Professional Bulletin for the AMEDD Community*

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*Commander, U.S. Army Medical Department  
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**Major General George W. Weightman**  
**Commanding General**



**Army Medical Department Center and School**  
**and Fort Sam Houston**

Major General George W. Weightman is a native of Eden Mills, Vermont. He received his Bachelor of Science Degree from the United States Military Academy at West Point in 1973 and was commissioned as a Lieutenant of Infantry.

After completing the Infantry Officers Basic Course, MG Weightman was stationed at Schofield Barracks, Hawaii, where he served in the 1st Battalion, 35th Infantry, 25th Infantry Division.

He was awarded a Doctorate of Medicine degree from the University of Vermont in 1982 and completed his Family Practice residency training at Eisenhower Medical Center, Fort Gordon, Georgia, in 1985.

After completing medical school and residency training in Family Practice, MG Weightman was assigned to Keller Army Community Hospital at West Point, New York, where he served as Chief, Department of Primary Care and Community Medicine. In 1989, he became the 82nd Airborne Division Surgeon and served with the All Americans during Operations Just Cause and Desert Shield/Storm. In 1991, he served as Family Practice Residency Director at Womack Army Medical Center before commanding the Medical Element, Joint Task Force Bravo, Soto Cano, Honduras. He then commanded the McDonald Army Community Hospital, Fort Eustis, Virginia, from July 1995 to July 1997 and from July 1997 to 1999, he commanded the 30th Medical Brigade in Heidelberg, Germany. In July 1999, he became the Chief of the Medical Corps Branch at United States Army Personnel Command, Alexandria, Virginia. From May 2002 to October 2002, MG Weightman served as Assistant Surgeon General for Force Projection. Major General Weightman returned to the XVIIIth Airborne Corps after serving from October 2002 to May 2003 as the Commanding General, 3rd Medical Command (Forward), and Coalition Forces Land Component Command Surgeon for Operation Iraqi Freedom. He served as Commanding General, 44th Medical Command/Corps Surgeon, XVIII Airborne Corps at Fort Bragg, North Carolina, from July 2003 to August 2004.

Additional military schools include the Infantry Officer Advanced Course, the Army Medical Department Officer Basic and Advanced Courses, Airborne and Jumpmaster Schools, the United States Army Command and General Staff College, and the United States Army War College.

Major General Weightman's awards include the Legion of Merit (three Oak Leaf Clusters), Bronze Star Medal (one Oak Leaf Cluster), Meritorious Service Medal (two Oak Leaf Clusters), Joint Service Commendation Medal, Army Commendation Medal (three Oak Leaf Clusters), Armed Forces Expeditionary Medal (with Bronze Arrowhead device), Southwest Asia Service Medal, Expert Infantry Badge, Expert Field Medical Badge, Senior Parachutist Badge with combat star, Honduran Parachutist Badge, Meritorious Unit Commendation, and Army Superior Unit Award. He is also a member of the Order of Military Medical Merit.

Major General Weightman is married with three children.

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# From the Commander, United States Army Medical Research and Materiel Command

Major General Lester Martinez-Lopez

I'm very pleased that the *AMEDD Journal* invited the USAMRMC to contribute a series of articles for a special edition about what we do for Army Medicine and for the Soldier, Sailor, Airman, and Marine.

This collection appropriately goes beyond our traditional efforts in medical research. Those who have been around the AMEDD for a few years know we have been involved in drug and vaccine development, medical chemical and biological defense research, and operational medicine studies for a long time. Some may know that we have carefully maintained relationships with a few host governments that allow us overseas opportunities for epidemiological studies and clinical trials for some of those drugs and vaccines. The articles about the Kenya laboratory, the USAMRIID, and the Military Operational Medicine Research Program deal with the current and future states of some of our traditional programs.

The other articles indicate how times have changed for the command in many areas. Bioinformatics is still a new science for many of us. However, we saw that there is the potential to apply bioinformatics, medical informatics and genomics in our medical research programs, and we have initiated a command-wide program to explore this potential. Doctor Reifman's article provides illustrative examples of how we might benefit from this initiative.

The contribution from our Congressionally Directed Medical Research Programs Office is a reminder that there are now two tracks for research funding that we deal with all the time – the traditional pathway whereby interested researchers read our Broad Agency Announcement, submit proposals, and, if they have what we need, receive research funding from the command's share of the Department of Defense (DOD) budget. The alternative pathway is for Members of Congress to write appropriations language that designates subject matter and recipients of research funds, and leaves management of the research grant process to us. Fortunately, some of the Congressional programs have great potential for leveraging new technology to enhance military medical readiness.

We operate in an open, very competitive marketplace. We collaborate with the other services, the non-DOD federal health



and research agencies, with academia, industry, and foreign entities – commercial, academic, and governmental. In a few areas, such as the establishment of the National Interagency Biodefense Campus at Fort Detrick, we are inventing new processes as we go. We have to have a comprehensive vision in these interactions, and we also have to be aware and informed in the legal, regulatory, political, and industrial arenas.

For this collection, we redirected an article written by our Comptroller office for the American Society of Military Comptrollers because we thought it deserved a wider audience. The Activity-Based Costing (ABC) Lessons Learned article shows not only that the USAMRMC took the ABC mandate seriously, but that, more importantly, the competitive environment in which we are currently operating requires that we be as advanced and effective in our business practices as we are in our scientific disciplines.

Finally, Command Sergeant Major Costa has contributed an overview of the command and each of its units in which he highlights the achievements of our Soldiers and civilian employees. His message is fundamental – we're nothing without the great people we have, and we need to keep growing them.

**From the USAMRMC  
Command Sergeant Major**



**CSM Domingo Costa**

As the Command Sergeant Major for the U.S. Army Medical Research and Materiel Command (USAMRMC) and Fort Detrick for the past year, I have had the distinct privilege to go throughout the command and witness firsthand how our Soldiers and civilians conduct their day-to-day business in a superb fashion. To see these young and seasoned group of leaders – Soldiers and civilians – volunteer, assist, deploy, research, provide logistical support to the warfighter, advise commanders, and perform their daily duties is second to none.

The Commander of the USAMRMC and Fort Detrick, MG Lester Martinez-Lopez, has a vision for the command: to deliver the best medical solutions for today and tomorrow, to enhance, protect, and treat the warfighter on point for the nation. Every day within the command, enlisted researcher Soldiers are called upon for their skills to go forward and provide technical assistance alongside a scientist or a doctor whose specialty is molecular or forensic medicine. These junior enlisted Soldiers, many of whom have bachelor's degrees and a number of whom possess master's degrees, are some of the brightest Soldiers this Army has in the ranks today. Their ability to assist and, in some cases, be a laboratory manager at their home station is not unheard of. These Soldiers are asking and volunteering to be a part of that world that, in some cases, others fear. We have Soldiers and civilians located throughout the U.S. and overseas. The USAMRMC consists of the headquarters, six medical research laboratories and institutes, and eight units that focus on medical materiel development, contracting, medical logistics management, health facility planning, information management, and management of congressional special interest programs.

One of our commands considered to be forward-deployed, the U.S. Army Medical Materiel Center-Europe (USAMMC-E), located at Pirmasens, Germany, provides the

best medical logistics support as the U.S. European Command's single integrated medical logistics manager for the military health care system. The center also supports the Department of State and Humanitarian Assistance Program and the U.S. Central Command in Southwest Asia. The commander acts as advisor to the chief surgeon, U.S. Army-Europe, on all medical logistics matters. The center has the vast responsibility of providing every level of medical logistics support to the warfighter serving in the Balkans, Iraq, Afghanistan, Africa, Europe, Italy, and other parts of the world. The command's ability to pack, ship, inventory, procure, and issue supplies on demand are second to none in the European theater. The center's level of expertise, which is rendered daily, has been seen and commended at every level of the Army leadership. "These Soldiers and civilians are forever vigilant and ready to provide the best service that one has to offer. Although we cannot be in the foxhole with the warfighter, we can provide them with the equipment and supplies that are very much needed on the battlefield. That is our reward and contribution to this fight against the global war on terrorism," said SFC Samantha Truesdale, detachment sergeant, USAMMC-E.

The USAMMC-E works seamlessly with the U.S. Army Medical Materiel Agency (USAMMA), based at Fort Detrick, MD. The connection and the rapport that these two agencies have with one another are critical to quickly receiving and responding to requests for supplies anywhere in the world. The USAMMA performs acquisition and life cycle management and materiel development for commercial and non-developmental items. It also serves as the logistician for medical materiel, command fielder, maintenance sustainment provider, and distribution manager for the Army Supply Class VIII Service Item Control Center, AMEDD National Maintenance Point, and medical treatment facility supporter. The agency conducts force projection and force sustainment operations, such as serving as the Army's pre-positioned medical stocks manager, being the agent for the Surgeon General's centrally managed contingency stocks and providing a medical logistics support team for the Army's pre-positioned stock, which are stockpiles of equipment and supplies to support worldwide requirements of any warfighting combatant command.

The USAMMA has responsibility for maintaining and managing the pre-positioned assets, including programming, budgeting, and executing for them. As part of the Army pre-positioned stocks program, and in concert with the Army Materiel Command's logistics support element, USAMMA's logistics support team exists to facilitate, when called upon, the handoff of class VIII medical materiel and nonmedical associated support items at a port or land-based facility in any theater. Comprised of military, civilian and contractor personnel, the Medical Logistics Support Team provides command and control, medical maintenance, general

maintenance, fielding of materiel, automation support, and contracting support.

Fielding teams, comprised of Soldiers and civilians, they travel to locations throughout the world to ensure that the units, combat support hospitals, field hospitals, general hospitals, and forward surgical teams that receive the equipment are adequately trained and prepared to use it. "Their hours on station are not measured by time but by the standard of familiarization that is required of them to safely operate the equipment. We will travel anywhere in the world to ensure that the equipment that is fielded to the units is received, inventoried, tested, and properly trained," said SFC Joseph Divito, detachment sergeant, USAMMA. The USAMMA provides medical services for information logistics systems, secondary inventory control activity for medical cataloging and standardization, and medical materiel quality assurance central coordinator for the services. The USAMMA's maintenance organizations provide medical equipment repair, overhaul, and refurbishment to support field medical units and medical facilities. Additionally, the medical maintenance divisions support USAMMA's role as the Army medical set assembly manager and AMEDD medical equipment sustainment program.

The Walter Reed Army Institute of Research (WRAIR) in Silver Spring, MD, conducts research on a range of militarily relevant issues, including naturally occurring infectious diseases, combat casualty care, operational health hazards, and medical defense against biological and chemical weapons. It is the Department of Defense's (DOD) lead laboratory for endemic infectious disease research and a crucial source of research support for medical product development.

The institute is directly responsible for the Better Opportunity for Single Soldiers program within the North Atlantic Regional Medical Command footprint. These Soldiers are committed to ensure that events, meetings, and functions are conducted on a quarterly basis and hold the strongest and most participated program on the East Coast. They also have a color guard team that is very much involved within the community and all military events. The team was called upon for a second year in a row to perform duties at the USAMRMC Commander's Conference in Baltimore, MD, because of their flawless presentation of the colors during the previous conference. "These Soldiers are of the highest caliber and they make us very proud," said SGM Sherry Lex, WRAIR.

The WRAIR oversees two research laboratory detachments and three overseas research laboratories. Located in Heidelberg, Germany, is the U.S. Army Medical Research Unit (USAMRU)-Europe, a subordinate unit to the WRAIR. Researchers there examine the psychological influences on the causes, cures, and prevention of psychiatric battle casualties.

They conduct basic and applied medical research focused on maintaining the health and readiness of the forward-deployed Soldier. The "Human Dimensions Teams" gather psychosocial and biomedical data with deployed units to determine the nature and extent of stressors, and identifies mediating factors that increase resiliency or vulnerability to stress. They advise commanders, senior Army leaders and planners, and the theater surgeon on critical aspects of mobilization, training, and leadership that promote effective Soldier and unit performance and aid in the prevention of psychiatric and stress-related casualties and performance declines. "These experts find themselves in redeployment platforms conducting psychological assessments on Soldiers returning home, ensuring that leaders at every level are made aware of any warning signs that Soldiers are displaying and educating leaders on what measures to take. Their level of expertise is remarkable and sought out throughout the Army," said SGT Casey Carr, noncommissioned officer in charge, USAMRU-E.

The USAMRU-Kenya, another WRAIR unit, is located in Nairobi. Researchers there develop and test improved means for predicting, detecting, preventing and treating worldwide infectious disease threats to deployed U.S. military personnel. They conduct global surveillance, training, research and response to emerging infectious disease threats. In addition, they conduct research for developing strategies to prevent HIV infection, conduct genetic research to help develop HIV vaccines and sponsor HIV prevention programs. They perform basic, clinical, and field research to develop and test improved products to detect, treat and prevent leishmania infection in deployed U.S. service members. "The relationship that was fostered 30 years ago continues to grow stronger among the Kenyan and local nationals wherever they come in contact with them," said MAJ Gina Marie Foglia, one of the military physicians currently working closely with the Kenyans in Kericho. Major General Lester Martinez-Lopez – accompanied by the Honorable Charity K. Ngilu, Minister of Health, Kenya, and William Bellamy, U.S. Ambassador, Kenya – celebrated the opening of the Kenya Medical Research Institute's Clinical Research Center in Kericho in a ribbon-cutting ceremony on 16 March 2004. The new state-of-the-art facility allows Kenyans to be tested for HIV at no cost and educate them on the prevention of the virus.

The WRAIR component of the Armed Forces Research Institute of Medical Sciences (AFRIMS), located at Bangkok, Thailand, conducts medical research, disease surveillance, and development and evaluation of medical products for military important infectious and tropical infectious diseases. Researchers monitor and assess potential infectious – especially emerging infectious diseases – and evaluate new drugs and vaccines for preventing and treating infectious diseases that are important to the military. They also develop and test new

forward-deployable rapid diagnostic methods along with investigating and testing new control measures against infectious disease vectors to interrupt disease transmission. They define the epidemiology of militarily important diseases endemic to tropical regions and advise the commander of the U.S. Pacific Command, and the U.S. ambassador to Thailand on tropical disease threats, as well as develop infrastructure and continue training, development and technology transfer to Thai medical research for Thai control and responsibility. "The Soldiers and civilians who conduct research and travel to remote locations within this country never once complain and are eager to find the solutions that will leverage the research that is much needed," said SFC Edward Williams, detachment sergeant, AFRIMS.

The U.S. Army Dental and Trauma Research Detachment (USADTRD), located in Great Lakes, IL, is another of WRAIR's units. It conducts world-class, unique and militarily relevant research for preventing, treating, and rehabilitating craniofacial trauma and infectious dental diseases. They formulate products that maximize the dental combat readiness and preparedness of the warfighter, minimize casualties due to dental infectious diseases, protect the head and neck from trauma, preserve tissue in the event of trauma, facilitate hard and soft wound healing, and minimize the logistic footprint of dental support in the deployed environment. They currently have a gum that is being tested in the laboratory that minimizes tooth decay and allows Soldiers in a field environment to go without dental hygiene for up to 3 days before tooth enamel breaks down. "These Soldiers are also very much involved in the pre-deployment and post-deployment platforms ensuring that all our Soldiers are taking care of their dental hygiene needs and are giving recommendations to prevent tooth decay," said SFC Angel Acosta, detachment sergeant, USADTRD.

The WRAIR's U.S. Army Medical Research Detachment, located at Brooks City Base in San Antonio, TX, determines the medical hazards of laser radiation and characterizes the effects of nonionizing radiation emitted by military systems on Soldier performance to determine medical triage and treatment of laser-induced injuries. Working with other services, researchers assure the protection and sustainment of Soldier health and safety in training, combat and special operations with military laser systems by developing medical triage and treatment for laser-induced ocular trauma, assisting in development of far-forward military medical doctrine and procedures for laser environments, determining the cellular and molecular mechanisms of laser-induced injury and repair, augmenting the laser bioeffects database to update safe exposure limits for military laser hazard assessment and eye protection specifications, evaluating and modeling vision and visual performance changes from laser exposure in military

scenarios, and developing and maintaining a laser accident and incident registry.

The U.S. Army Aeromedical Research Laboratory, located at Fort Rucker, AL, conducts research on health hazards of Army aviation, tactical combat vehicles, selected weapons systems and airborne operations and develops countermeasures for these risks. Its researchers recommend standards and design criteria for avoidance of health hazards from noise, acceleration, impact, and visual demands of military systems, and they define measures to offset hazards. Located at the home of Army aviation, the laboratory's scientists assess the impact on health and performance of stress and fatigue in personnel operating military systems and develop countermeasures and assist in the development of criteria upon which to base standards for entry and retention in Army aviation specialties. Researchers there also assist other USAMRMC laboratories and institutes in determining the bioeffects of laser systems, the impact of continuous operations on individual and crew performance, improved means of patient evacuation, and the militarily-relevant side effects in medical products. They also test and evaluate medical equipment used in aeromedical evacuation. Additionally, they assess current life-support equipment to identify causes of failure and devise improved design criteria and assist the combat developers and materiel developers of new Army aviation and tactical combat vehicle systems to recognize and eliminate health hazards as early as possible in the development cycle. They perform collaborative research with DOD and other federal agencies on medical research and development issues of common concern. "I am amazed to watch the level of professionalism when the enlisted researchers work closely with the subjects (volunteers) during the protocols. Their ability to understand and to explain to the subjects what the desired result that the institute is looking for is incredible," said SFC Ernest Hiltz, 91KP9, enlisted researcher.

The U.S. Army Research Institute of Environmental Medicine, located at Natick, MA, conducts basic and applied research to determine how exposure to extreme heat, severe cold, high-terrestrial altitude, occupational tasks, physical training, deployment operations, and nutritional factors affect health and performance of military personnel. Researchers at the institute are also responsible for providing recommendations to the Soldier Support Center for the design of the battle dress uniform, parachuting equipment, and aerial delivery equipment. They also provide input that comes from the field for meals ready to eat, giving recommendations to the designer of the field mess facility. They also give input on new tents used in the field. "Our Soldiers will do all they can and to the best of their ability to release to the field the very best equipment to accomplish the mission for those who are making it happen for us," said SFC David Welch, 91KP9, enlisted researcher.



The U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), located at Aberdeen Proving Grounds, MD, develops medical countermeasures to chemical warfare agents and trains medical personnel in the medical management of chemical casualties. The Soldiers are responsible for training the Central Intelligence Agency, Criminal Investigation Division, Drug Enforcement Agency, Navy SEALs, Special Forces units, and physicians of all specialties. "The enlisted Soldiers of this command are true professionals, and their ability to train the elite and to be respected by them, regardless of their rank, is a testament to their level of expertise. Knowing the risks that are involved in the chemical and biological labs that they are exposed to day in and day out never once causes them to regret what they do for this Army and the nation that they serve," said MSG William Cafferky, NCOIC, USAMRICD.

The U.S. Army Center for Environmental Health Research (USACEHR), located at Fort Detrick and a subordinate unit to USAMRICD, conducts basic and applied research to enhance force health protection from environmental health hazards, including toxic industrial chemicals and materials. Scientists conduct research to develop and validate new bioassays and technologies for deployment health surveillance, provide early detection of environmental hazards through the development and fielding of aquatic biomonitoring technologies, and develop new water and food testing technologies to ensure the safety of provisions for deployed U.S. forces. "We have an initiative with the European theater to possibly initiate a pilot study, a sentinel environmental biomonitoring process, to detect early presence of various metals, chemical, and other material that may find its way into potable water systems whether intentionally introduced in the system (terrorist activity) or as a result of an accident. This will involve pumpkinseed fish (blue gill) that will be the guinea pig placed in a biomonitoring device to detect the contaminant. This is a system that is being used in New York City, and I am convinced that it will work in Europe too," said LTC Rodger Martin, Commander, USACEHR.

The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), located at Fort Detrick, conducts basic and applied research on biological threats resulting in medical solutions to protect the warfighter. The institute provides subject matter expertise and available research reagents to local, state, and federal laboratories involved in developing and improving systems for disease surveillance, reporting, and diagnosis. The USAMRIID also conducts collaborative field studies to map the distribution of emerging diseases or to test new diagnostic methods. Currently, the USAMRMC has a proposal to fund construction of a new USAMRIID facility as part of a bio-defense campus being created at Fort Detrick. The U.S. Army Health Facility Planning Agency leads the command's effort to make the new USAMRIID research facility a reality. The new

state-of-the-art campus will be the nation's, and perhaps the world's, leading research center on biological defense matters. "The Soldiers and civilians, alongside the scientists and researchers are the very best at their skill in our Army medical department. They work in the biosafety levels one through four (laboratories) where most human beings fear the most because of the exposures to infectious agents in a laboratory or field setting. They all know the risks that are involved, but they also understand the value added, and know how much the work they do means to the public," said SGM Edwin Lewis, USAMRIID.

The U.S. Army Institute of Surgical Research (USAISR), located at Fort Sam Houston, provides combat casualty care medical solutions and products for injured Soldiers from self-aid to definitive care across the full spectrum of military operations. They are responsible to the commander of the Brooke Army Medical Center for managing the DOD's only burn center and trauma division combining burn, trauma and critical care services. They provide state-of-the-art burn, trauma, and critical care to DOD beneficiaries around the world, as well as burn special medical augmentation response teams. "The enlisted Soldiers of the team are directly responsible for the care and rehabilitation of their assigned patients and see their recovery all the way through discharge. They have the innate ability to detect infections and recommend treatment to their nurse in charge or physicians because of the intense training that they receive. They are also required to train and test under the same standards as the nurses for advance trauma life support, pediatric trauma life support, and pre-hospital trauma life support," said 1SG Calandria Hypolite, USAISR.

The U.S. Army Medical Materiel Deployment Activity, located at Fort Detrick, provides program management for the development of new drugs, vaccines, and medical devices. It serves as a sponsor's representative to the Food and Drug Administration for all investigational new drugs held by Office of The Surgeon General and the executive agent, Investigational New Drugs for Health Protection.

The U.S. Army Medical Research Acquisition Activity at Fort Detrick provides contracting and assistance support for the USAMRMC extramural research and development program to all of the USAMRMC and Fort Detrick units located within the U.S. and overseas. They provide advice and guidance to contracting officers, representatives, research area managers, laboratory commanders, and liaisons as appropriate. They provide procurement training for Army Medical Department officer interns through a 2-year program, which includes formal instruction and practical experience.

The U.S. Army Medical Information Technology Center, located at Fort Sam Houston, TX, is the hub that provides full spectrum information technology systems, architecture,

acquisition, and life-cycle management for the Army Medical Department. The center helps link the USAMRMC commands that administer DOD congressional programs, conduct medical research and development, monitor logistics and acquisition management at the Army level, and provide advance technologies that directly impacts the Army across the spectrum.

The Telemedicine and Advanced Technology Research Center (TATRC) also works in the information technology arena, assessing new products and technologies for their potential to enhance Army medicine. The TATRC supports new technology development, and performs rapid prototyping

and test bed evaluation of new technologies. The Battlefield medical information system-tactical, an application that allows medics to record medical information on a PDA-type computer, is a TATRC product currently in use by the Stryker Brigades in Iraq.

A complex organization of many subordinate units, staffed by cutting edge scientists, the USAMRMC focuses its resources on the warfighter on point for the nation. Leaders of the command know that a critical part of this mission is to train, develop, and mentor the Soldiers and civilians assigned to the command. Without them, the command's many contributions to medical readiness would not be possible.

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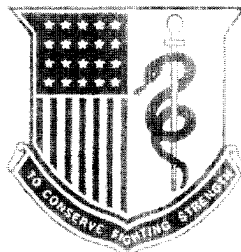
**LTC (P) Patricia Patrician, AN**

Lieutenant Colonel (P) Patrician has replaced COL Janet R. Harris as the Army Nurse Corps representative. LTC Patrician is the Chief, Department of Nursing Science, Academy of Health Sciences, U.S. Army Medical Department Center and School, Fort Sam Houston, TX.



**COL Ney M. Gore, MC**

Colonel Gore replaces COL (now BG) Carla G. Hawley-Bowland. COL Gore is the Medical Corps Staff Officer, Corps-Specific Branch Proponency Office, U.S. Army Medical Department Center and School, Fort Sam Houston, TX.



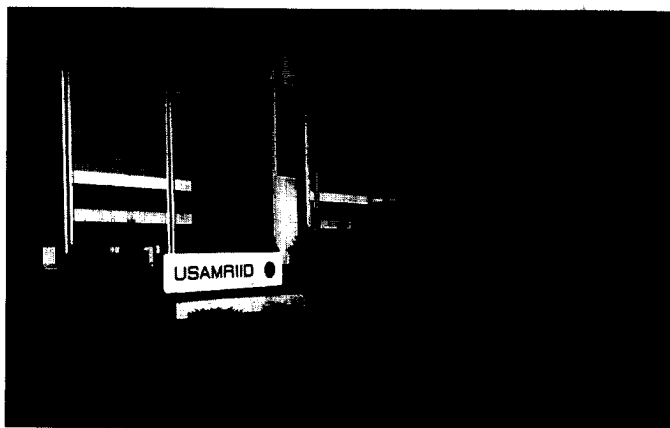
# USAMRIID: The Cornerstone for Medical Biodefense

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*The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) conducts basic and applied research on biological threats resulting in medical solutions to protect military service members. The Institute is the lead medical research laboratory for the U.S. Biological Defense Research Program. The Institute plays a key role as the only laboratory in the Department of Defense (DOD) equipped to safely study highly hazardous infectious agents requiring maximum containment at biosafety level 4. As the center of excellence for DOD medical biological defense research, USAMRIID's challenge is to maintain its world-class scientific and technology base while being responsive to its primary customer – the warfighter.*

## Introduction

For over 35 years, the USAMRIID, Fort Detrick, MD, has been the DOD lead laboratory for medical biological defense. While the laboratory's core mission is to conduct basic and applied research on biological threats resulting in medical solutions to protect the warfighter, it supports all phases of medical product development for biodefense, education and training, and operational medicine response. The USAMRIID also provides a critical capability to the Army's Medical Infectious Disease Research Program as the only DOD laboratory equipped to study highly hazardous viruses that require containment at biosafety level 4. The USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.



*USAMRIID Crozier Building.*

The USAMRIID's mission has become more important as the nation faces a heightened risk of bioterrorism. Medical products once developed for military use are now leading candidates for protecting civilian populations as well. In addition to medical countermeasures, information is a key product of the institute's research as evidenced by the hundreds of publications and scientific presentations prepared by USAMRIID scientists

each year. As a founding member of the Centers for Disease Control and Prevention (CDC)-sponsored Laboratory Response Network, USAMRIID provides "national" laboratory capabilities and specialized medical and scientific consultation on bioterrorism issues across the U.S.

Over the past 3 years, USAMRIID has emerged as the cornerstone of the nation's interagency biodefense strategy. A series of U.S. House and Senate reports since September 2001 not only acknowledges USAMRIID as the military's premier biodefense laboratory, but also recognizes that the unique biocontainment facilities and expertise of USAMRIID are a national asset, providing indispensable support to the federal biodefense research system.<sup>1-3</sup> Efforts are currently underway to establish a National Interagency Biodefense Campus at Fort Detrick that will consist of several federal laboratories, including USAMRIID. Close proximity and shared resources will facilitate interagency research on medical countermeasures, benefiting both civilian and military populations.

## History and Infrastructure

The USAMRIID was established by General Order No 6, dated 27 January 1969, Office of The Surgeon General of the Army, with a mission to develop medical defenses against biological warfare threats.<sup>4</sup> However, the roots of the laboratory extend to the U.S. Army Medical Unit at Fort Detrick, which was established in 1956 as the first U.S. medical organization dedicated solely to medical biological defense.<sup>5</sup> The modern USAMRIID was opened in 1971-1972 after the dissolution of the U.S. offensive biological warfare program. The current facility consists of 13 buildings with approximately 356,000 gross sq ft of research laboratory and administrative space. The USAMRIID houses the nation's largest collection of biological safety level (BSL) 4 space (about 15,000 sq ft) and the DOD's largest collection of BSL 3 space (about 50,000 sq ft). It is the only DOD research entity in the U.S. that possesses aerosol-testing facilities for the most pathogenic biological agents and

toxins. The USAMRIID's animal care facilities are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. In addition to its unique containment laboratories, USAMRIID also manages the large animal care facility for producing diagnostic and detection reagents. During the first Gulf War in 1991-1992, this facility produced a great deal of equine anti-toxin against seven types of botulinum neurotoxin. The USAMRIID's field laboratory training facility trains laboratory technicians from all services on the field identification of biological threats.

Originally built for approximately 325 scientists and administrative staff, the facility now supports over 740 military, civilian, and contractor personnel. Over 200 staff members have postgraduate degrees in medicine or veterinary medicine, or PhDs in a broad array of allied medical sciences. The USAMRIID's research also is supported by specialists in safety, biosecurity, security and regulatory affairs.

### Medical Product Development

The USAMRIID is a DOD "tech base" organization, where vaccine candidates, diagnostics, and therapeutics are discovered, refined, and taken through various stages of testing before hand-off for advanced development by the Joint Vaccine Acquisition Program, the Joint Program Executive Office-Chemical Biological Defense, or a civilian organization. The

USAMRIID currently has a research budget of \$50 to 60 M annually, and over 80% of its activities directly support the DOD. Other customers include the U.S. Army, the Department of Homeland Security (DHS), the Department of Justice, and the Department of Health and Human Services. Since 1969, USAMRIID scientists, who identify and evaluate one new medical countermeasure per year on average, have developed over 20 medical research products, including vaccines, prophylactic and therapeutic drugs, diagnostic systems, and information to safeguard the health of service members (Table 1). Taking advantage of advancements in biotechnology over the past decade, USAMRIID has developed candidate vaccines for botulinum neurotoxins, Venezuelan equine encephalitis (VEE), plague, staphylococcal enterotoxins A and B, and *Hantaviruses*, as well as a next-generation anthrax vaccine and rapid diagnostic.<sup>6-12</sup> About a dozen other vaccines developed at USAMRIID are maintained in investigational new drug (IND) status and are used to vaccinate at-risk personnel in the laboratory and in the field where necessary.<sup>13</sup> Several of these products, managed by Army MEDCOM SMART Teams, were made available through contingency clinical protocols to warfighting commands during the 2003 Gulf War.

While most of USAMRIID's research products were intended for military use, civilian agencies have often depended upon USAMRIID products or information in response to bioterrorism. The National Institute of Allergy and Infectious

IND Products	Products In Advanced Development	Emerging Products
<ul style="list-style-type: none"> <li>• Tularemia (LVS) Vaccine</li> <li>• VEE Vaccines, TC-83 (attenuated) and C-84 (inactivated)</li> <li>• Eastern Equine Encephalitis (EEE) Vaccine</li> <li>• Western Equine Encephalitis (WEE) Vaccine</li> <li>• Pentavalent Botulism Toxoid</li> <li>• Smallpox Vaccine</li> <li>• (cell culture derived vaccinia virus)</li> <li>• Botulinum Antitoxin</li> <li>• (human and horse)</li> <li>• Vaccinia Immune Globulin</li> <li>• Ribavirin</li> <li>• Rift Valley Fever Virus Vaccine</li> <li>• Chikungunya Virus Vaccine</li> <li>• Junin Virus Vaccine</li> <li>• Q Fever Vaccine</li> </ul>	<ul style="list-style-type: none"> <li>• Next Generation Anthrax Vaccine (rPA)</li> <li>• Botulinum Neurotoxin Bivalent Vaccine (A/B)</li> <li>• VEE Virus (V3526) Vaccine</li> <li>• Plague Vaccine (F1-V)</li> <li>• Joint Biological Agent Identification System (JBAIDS)<sup>1</sup></li> <li>• Cidofovir Treatment of Smallpox</li> </ul>	<ul style="list-style-type: none"> <li>• Staphylococcal Enterotoxin Vaccines (A/B)</li> <li>• <i>Hantavirus</i> Vaccines</li> <li>• Botulinum Neurotoxin Heptavalent Vaccine</li> <li>• Next-Generation Immunodiagnostics</li> <li>• Next Generation EEE/WEE Vaccines</li> <li>• Pan Filovirus Vaccines</li> <li>• Generation After Next Anthrax Vaccine</li> </ul>

<sup>1</sup>JBAIDS platform will include diagnosis and detection assays for all of the most important biological agents and infectious diseases of military importance.

Table 1. USAMRIID Medical Products Portfolio

Diseases (NIAID) and commercial manufacturers have sought USAMRIID's biodefense medical products for civilian applications. During the past 2 years, USAMRIID has successfully moved products into advanced development through a partnership with NIAID. The NIAID has supported the development of the next-generation anthrax vaccine, called recombinant PA (protective antigen), as well as multivalent vaccines for botulinum neurotoxins.<sup>6,9</sup> The NIAID is considering the development of vaccines against plague and Rift Valley fever based upon technologies developed at USAMRIID.<sup>8,14</sup> Similarly, USAMRIID scientists are collaborating with the National Institutes of Health (NIH) to identify and develop therapeutics for a number of agents, including Ebola virus, several toxins, SARS (severe acute respiratory syndrome), and Orthopoxviruses.<sup>15-18</sup>

### Training and Education

Research performed at USAMRIID is translated into state-of-the-art information for medical providers through our training and education programs.<sup>19</sup> The USAMRIID and the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) jointly conduct the Medical Management of Chemical and Biological Casualties Course. The course is designed for Medical Corps and Nurse Corps officers; physician assistants; Medical Service Corps officers in specialties 67B, C, or E; and other selected medical professionals. Classroom instruction, laboratory work, and field exercises prepare graduates to effectively manage casualties of chemical and biological agent exposure. Classroom discussion includes the history and current threat of chemical and biological agent use, the characteristics of threat agents, the pathophysiology and treatment of agent exposure, and the principles of field management of threat agent casualties. The course is available via several distance-learning products, including satellite broadcast, video teleconference, and videotape series. Educational products produced by USAMRICD and USAMRIID are the only source of advanced individual education in the medical management of chemical and biological warfare agents for military medical personnel. Since 1991, USAMRIID has also participated in the pre-deployment training of table of organization and equipment medical units in important theaters of operation. Over 100,000 students have been trained since the program was established.

Postgraduate PhD scientists may receive medical research training through USAMRIID's National Research Council (NRC) fellowship program. Candidate NRC fellows and associates develop competitive proposals related to USAMRIID's core mission and are integrated into existing research activities. Research fellows train with highly qualified senior scientists for 1 to 3 years. The NRC fellowship program has been an exceptional source of productive and innovative

scientists, who often contribute significantly to the development of new medical countermeasures. The NRC fellows and associates who have completed the program often continue to support USAMRIID, the medical biological defense research program, or the medical infectious disease research program as full-time civilian or contractor employees. The USAMRIID currently supports 22 PhD fellows and is developing plans to expand programs to train pre-doctoral students as well.

After the first Gulf War in 1991, military planners recognized the need for confirmatory laboratories that could provide high-level of confidence for identifying selected biological threats. A variety of forward-deployed laboratories managed by the services provide theater commanders with this unique capability. Since 1997, USAMRIID has been providing "wet" laboratory training to service members selected to serve in theater-level confirmatory laboratories, such as the 520th Theater Army Medical Laboratory. The USAMRIID sponsors a flexible collection of teaching modules under a unifying set of operational principles in the Field Identification of Biological Warfare Agents Course. The course is conducted in a realistic field laboratory setting, duplicating the austere conditions that might exist in warfighting theaters. Course materials and modules are tailored to student and unit requirements. Over 100 students from all three services have completed the course. With the addition of new facilities, USAMRIID can now offer seven full courses and three abridged managers' courses each year.

### Response to Emerging Biological Threats

In addition to its primary mission of biological defense, USAMRIID is often called upon to respond to infectious disease outbreaks (Table 2). Working with our partners in the CDC and the World Health Organization, USAMRIID scientists have played contributing roles to evaluate outbreaks of VEE in Central America, *Hantavirus* pulmonary syndrome in California, West Nile fever in New York, and Ebola hemorrhagic fever in Africa. Immediately after the 11 September 2001 attacks, USAMRIID was the only national laboratory to provide round-the-clock analytical support to federal and state authorities. After the anthrax letter attacks, USAMRIID was used as a confirmatory site for identifying and characterizing anthrax spores. Over 8 months, USAMRIID processed over 30,000 samples and performed approximately 260,000 assays to support environmental surveillance, respond to potential biological threats, and support remediation efforts.

### Future

Recognizing USAMRIID's critical role in the nation's biodefense, Congress has directed several federal departments to coordinate their programs and capital investments in

1969	Venezuelan equine encephalitis, Honduras
1971	Venezuelan equine encephalitis, Central America, Southern Texas
1974	Eastern equine encephalitis, Patuxent, MD
1977	Rift Valley fever, Egypt
1983	Chikungunya fever, Indonesia
1988	Infant botulism, San Francisco
1988	Rift Valley fever, Senegal/Mauritania
1989	Simian hemorrhagic fever, NM
1990	Reston Ebola hemorrhagic fever, Reston, VA
1993	Hantavirus acute pulmonary syndrome, UT, CO, NM, AZ
1993	Rift Valley fever, Egypt
1995	Ebola hemorrhagic fever, Zaire
1995	Venezuelan equine encephalitis, Colombia
1996	Ebola Reston hemorrhagic fever, Alice, TX
1997	Ebola hemorrhagic fever, Ivory Coast
1999	West Nile virus, NYC
2000	West Nile virus, all states (except AK, HI, OR, WA)
2000	Anthrax, MN
2000	Potential Ebola hemorrhagic fever case, Uganda
2001	Anthrax, WA, NY, FL
2003	SARS (CA, NJ, NM, NC, PA, UT, VA)
2003	Monkeypox, IN, IL, WI
2003	Malaria outbreak among U.S. Marines, Liberia

Table 2. USAMRIID Responds to Emerging Infections Disease Outbreaks

biodefense research, and to consider co-locating to Fort Detrick to leverage the unique capabilities of USAMRIID. The NIAID and the DHS will build new biodefense laboratories at Fort Detrick in the near future. Congress also has directed the U.S. Department of Agriculture (USDA) to study the need for a shared BSL three laboratory with the Army.

The National Interagency Biodefense Campus at Fort Detrick will take advantage of the combined resources of five federal partners, the NIH, the National Cancer Institute, the DHS, the USDA, and the DOD, to provide the biodefense medical products the nation needs in the future. Collectively, these laboratories with complementary scientific goals will collaborate on developing a comprehensive understanding of biological agent characteristics, elucidating the disease process, and developing products to reduce risks to human health and agricultural productivity. Coordination of these proposed activities will take place through an established Fort Detrick interagency committee.

Efforts are also underway to replace USAMRIID's aging facility. In the aftermath of the anthrax attacks in October of 2001, Congress directed the Secretary of the Army to conduct a feasibility study to determine the infrastructure requirements and associated costs needed to accommodate USAMRIID's expanded role in the nation's biodefense. The proposed new USAMRIID laboratory calls for two main stages of construction. Stage one will house the most critical DOD assets in 676,000 sq ft of laboratory space to decompress overcrowded

biocontainment laboratories and expand medical test and evaluation (TE) capacity to meet immediate DOD and national demands. Stage two will house the balance of USAMRIID's expanded mission and provide incremental expansion to meet the projected national requirements for medical TE generated by ongoing increased investments in biodefense basic sciences. The DOD is finalizing program requirements and will make the necessary funding requests for stage one within the context of DOD programs in combating weapons of mass destruction and biodefense. Definitive scope and funding requirements for stage two will require further study of interagency programs. The federal medical biodefense partners at DHS, NIH, and USDA strongly support the critical requirement to modernize USAMRIID, and are actively participating in the creation of the National Interagency Biodefense Campus at Fort Detrick.

## Summary

For 35 years, USAMRIID has responded to epidemics and developed protective medical countermeasures against the world's deadliest diseases. It provides the DOD and the federal biodefense base with unique facilities and expertise to safely conduct critical basic science, aerosol studies, testing and evaluation, clinical research and treatment in FDA-regulated, high-level biocontainment environments. The USAMRIID innovations continue to yield state-of-the-art vaccines, drugs, and diagnostics that protect the military and American citizens from anthrax, smallpox, botulism, Ebola, malaria, and other biological threats. In short, USAMRIID is a key national asset to the global war on terrorism — a cornerstone for medical biological defense.

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# United States Army Medical Research Unit-Kenya

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*The U.S. Army Medical Research Unit-Kenya (USAMRU-K) is part of the Walter Reed Army Institute of Research (WRAIR). The WRAIR employs a cadre of highly skilled, exceptionally motivated, world recognized scientists, physicians, technical and administrative staff capable of effectively developing and incorporating cutting edge technologies to produce state-of-the-art medical solutions that address militarily relevant health issues, such as infectious diseases, combat casualty care, military operational medicine, and medical chemical and biological defense.*

## Introduction

The USAMRU-K is a Special Foreign Activity of the WRAIR with a mission to develop and test improved products for the diagnosis, treatment, and prevention of infectious disease threats to deployed service members. It also undertakes surveillance activities to identify and develop response strategies for emerging infections that have the potential to impact readiness, mission accomplishment, or homeland security. Such activities must be undertaken in overseas locations where the incidence of infectious diseases is high enough to permit the evaluation of new drugs, vaccines, or diagnostic devices.

The USAMRU-K is the only U.S. Department of Defense (DOD) infectious disease laboratory in sub-Saharan Africa. This region of the world is of interest because it is replete with known and unidentified vector borne infectious diseases but lacks the infrastructure and expertise to detect, treat, characterize, or control their transmission. In addition to its high infectious disease burden, sub-Saharan Africa is afflicted by cross-border political instability and internal insecurity, increasing the likelihood of U.S. intervention for peacekeeping or other missions. Kenya is a longtime ally of the U.S. with shared values and a relatively functional political, commercial, educational, and medical research infrastructure.

Several infectious diseases of military relevance are endemic to Kenya. Malaria predominates in the coastal and western lowlands. The highlands, previously considered malaria-free, can experience epidemic or imported malaria. Leishmaniasis is focally distributed in the Baringo district, in the Machakos district, and in the arid but vast northeastern regions of the country. Enteric pathogens cause significant morbidity and mortality in poor communities in urban and remote areas where opportunities for zoonotic diseases prevail. In addition, West Nile virus, dengue virus, and other military-relevant infectious diseases are present in the region.

Infrastructure investments have been made that position

USAMRU-K to play a far-forward role in the execution of the WRAIR mission of product development for the warfighter. Over several decades of collaboration, internationally accepted systems have been put in place to regulate and monitor joint operations. Human use protocols and animal use protocols are approved by duly constituted local and U.S. scientific, animal use, or human use and ethical review committees, prior to execution. Designated monitors representing all the sponsors monitor the ongoing clinical trials. Laboratory and clinical studies meet and exceed international standards set by Good Laboratory Practice and Good Clinical Practice regulations and are conducted with a view towards submission to the U.S. Food and Drug Administration for licensure. Participation of local personnel is encouraged, including participation at the highest administrative level and leadership at the principal investigator level. Local institutional strengthening activities are reflected in all USAMRU-K activities. Study results are shared with host nation partners and with international organizations, and are published in peer-reviewed journals; intellectual property rights are respected.

## History

In 1969, WRAIR was invited by the Kenyan Government to undertake research in trypanosomiasis in the Lambwe valley. The success of the program led to the establishment, by Cooperative Agreement, of a broader endeavor at the Kenya Medical Research Institute (KEMRI) in 1979 (Figure 1). The USAMRU-K was the first American organization housed at KEMRI, which is the principal research component of the Kenya Ministry of Health. This Cooperative Agreement initially covered malaria immunology and vaccine development, microbiology, drug development, and vector studies. In the later years of the agreement, allowance was made to carry out initial work in Leishmania transmission, arbovirus transmission, enteric pathogens, and HIV. The malaria work is centered in Nyanza province around the city of Kisumu and its environs. It comprises malaria immunological studies, studies of molecular mechanisms for susceptibility to malaria-induced



severe anemia of pregnancy, and malaria vaccine trials. Microbiology and drug development includes drug sensitivity testing for antimalarials and antibiotics, diagnosis of enteric and viral pathogens, and vector surveillance for transmissible agents. Investigations are also undertaken on the coast, in urban slum communities, and in remote locations in Entosopia. The scope of work ranges from field studies to basic research on the diseases of interest.



*Fig 1. Headquarters, KEMRI in Nairobi, Kenya.*

The USAMRU-K also participates in the Global Emerging Infections Surveillance and Response System (GEIS). A surveillance network for the country and for the region is being established in collaboration with the U.S. Centers for Disease Control and Prevention, and the World Health Organization (WHO) Centre for Haemorrhagic Viruses.

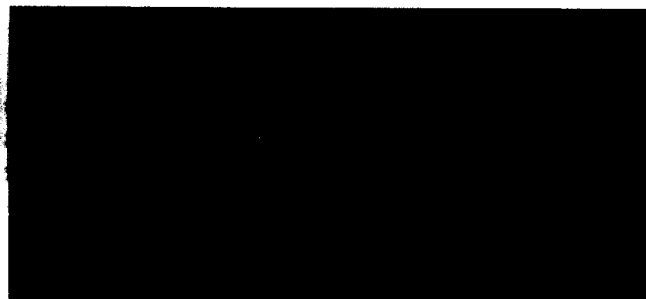
### **Malaria Immunology**

The USAMRU-K tests and develops drugs and vaccines for the prevention and treatment of malaria in the warfighter. Studies of semi-immune and nonimmune populations in malaria-endemic areas increase our understanding of how malaria causes death and disease.

The USAMRU-K's operations in the Kisumu area are based in two facilities. The Walter Reed Project Kombewa Clinic is a newly constructed clinical research center with 4,000 ft<sup>2</sup> of floor space (Figure 2). It contains clinical and research laboratories, storerooms, consultation rooms, overnight on-call rooms, data entry rooms, one large dining room, and a conference facility. The Kisian research laboratory has approximately 1,000 ft<sup>2</sup> of floor space. It consists of a parasitology/culture laboratory, an immunology laboratory, an entomology/microscopy laboratory, a conference/library room, and an administrative office.

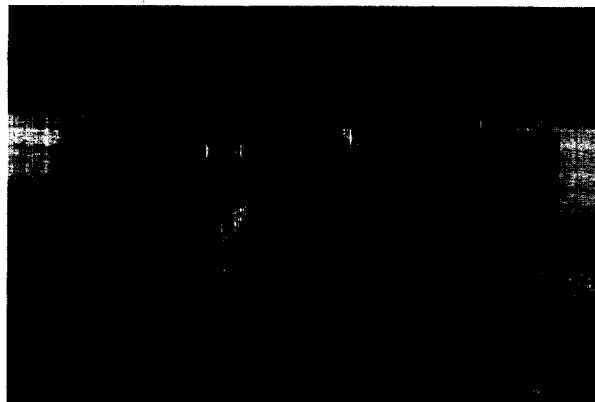
The malaria vaccine and drug program is based at the Walter Reed Project Kombewa Clinic. This center is dedicated to the study of the epidemiology of malaria transmission in the local population through cross-sectional surveys and longitudinal cohort studies. Using this knowledge, we can

design and plan the execution of malaria vaccine and drug trials. Currently, the leading vaccine candidate being investigated is the merozoite surface protein 1 which is found on the surface coat of malaria merozoites. Other vaccine antigens that may be investigated in the near future include the apical merozoite antigen 1 and the liver stage antigen 1. Several drug prophylaxis trials are being contemplated including the novel anti-malarial drug tafenoquine as well as combinations of older drugs such as chloroquine and azithromycin. The program relies heavily on the funding from partnership between DOD and nonprofit organizations such as the Malaria Vaccine Initiative, and industrial partners such as Glaxo-SmithKline.



*Fig 2. Kenya-Kombewa Clinic.*

The malaria pathogenesis program is based at USAMRU-K's research laboratory in Kisian and at local hospitals such as the Nyanza Provincial General Hospital and the Kisii District Hospital. It seeks to achieve a better understanding of the pathogenesis of severe malarial anemia and cerebral malaria, two of the deadliest complications of *P. falciparum* malaria. For this purpose, hospital-based case-control studies are being implemented to compare children with severe malaria to children who do not develop severe malaria to identify genetic and phenotypic differences between these two populations (Figure 3). A major area of research is in the role of red cell complement regulatory proteins and complement in the pathogenesis of these two conditions. The program is supported by grants from the National Institutes of Health, the Fogarty International Center, and the WHO.



*Fig 3. Schoolchildren in rural Kenya.*

## Anti-Malarial Drug Discovery

The USAMRU-K also conducts scientific research directed toward the development of new anti-malarial agents to protect U.S. forces deployed to malaria endemic areas. Scientific research is conducted in two separate laboratories with distinct but complimentary efforts. The Malaria Drug Screening Laboratory conducts research on malaria drug discovery and drug resistance. Malaria drug discovery efforts currently test natural products, both as plant extracts and purified compounds for their ability to kill the malaria parasite in culture. These efforts are aimed at identifying a naturally produced compound that can be transitioned into advanced development as a new anti-malarial drug. Drug resistance research is in support of the USAMRU-K GEIS program, which has established sites in several geographically distinct areas of Kenya and Uganda where malaria parasites are collected, transported to the laboratory, and tested for their drug susceptibility. This laboratory also will support malaria drug clinical trials with the culturing and testing of field isolates of malaria. The Molecular Malaria Laboratory conducts scientific research aimed at understanding the molecular mechanisms of drug resistance. Several genes are well characterized as containing mutations that confer resistance to many currently prescribed anti-malarial drugs. Identification of these mutations allows our laboratory to assess the severity of drug resistant malaria and provide indications as to the effectiveness of current and future anti-malarial therapies. This laboratory also conducts studies aimed at identifying malaria enzymes that can be targeted for drug discovery.

## Entomology

The USAMRU-K develops and tests improved means for predicting, detecting, and preventing arthropod-borne disease threats to military and civilians in East Africa. The program conducts tests of products and vector-control systems, and investigates emerging arthropod-borne diseases. Study sites are developed and maintained to provide field-testing for products such as vector surveillance devices, insecticide formulations, and repellents. Current field test sites include: the Kisumu area in western Kenya, for repellent evaluations and malaria vector control studies; Kilifi in coastal Kenya, for dengue vector surveillance and control studies; and the Baringo District in the central Rift Valley Province, for *Leishmania* vector control studies. In addition to testing products, USAMRU-K has an active program aimed at improving our understanding of the threat posed by emerging infectious diseases in Kenya. Current or proposed investigations of emerging threats include: determination of potential vectors of malaria in a highland area of Kenya, Kibera in Nairobi; studies of *Rickettsia africae* in the Masai Mara Region of Kenya including establishment of pathogen presence, determination of host/vector ticks, and

modeling of vector distribution using Earth-orbiting satellite data; and entomological studies of the prevalence of arboviruses along the coastal area of Kenya.

Execution of the entomology program is primarily supported by the Military Infectious Disease Research Program, Fort Detrick, MD, and by the DOD Global Emerging Infections Surveillance and Response System program in Kenya. Key relationships have been established with the National Aeronautics and Space Administration/Goddard Flight Center, Beltsville, MD; the Kenya Meteorological Department, Nairobi; the International Centre of Insect Physiology and Ecology, Nairobi; the International Livestock Research Institute, Nairobi; and the Kenya Pest Control Products Board, Nairobi.

## HIV

The USAMRU-K conducts clinical research to develop prevention strategies for HIV infection and genetic research to develop HIV vaccines (Figure 4). It is the primary field station for the U.S. Military HIV Program in Africa. The USAMRU-K provides regional coordination between programs in Uganda, Tanzania, and Kenya. The primary mission of the project is to develop and test vaccines based on the genetics and subtypes or clades of the viruses prevalent in this region of the world. Clinical evaluation of the role of clades A, C, and D in the HIV epidemic in the region will permit the development of HIV vaccines for testing in East Africa. The objectives of the project are: (1) to estimate the incidence and prevalence of HIV, (2) to characterize the risk factors associated with HIV infection, (3) to determine the viral clades and recombinations of HIV-1 in Kenya, (4) and to characterize the kinetics of HIV-specific immune responses, CD4 counts and viral loads in early HIV infection and in the face of malaria co-infection.



Fig 4. The Walter Reed Project is an HIV education, screening, and prevention program in the Kenyan highlands.

In addition to conducting research, the program also sponsors HIV prevention programs, as part of the regional effort

to identify populations that may be candidates for the study of HIV vaccines in the future. Local communities are instructed about HIV through "barazas" where the staff performs drama relating to HIV risk behaviors and illness in Kiswahili and English. Additionally, the program conducts workshops to update the local medical community about HIV/AIDS and facilitates the development of other prevention programs such as mother-to-child transmission and HIV in the workplace. The Program collaborates with the Boston University School of Public Health in a study to estimate the impact of morbidity on labor productivity in the Kenya Highlands.

### Emerging Infections

The U.S. DOD GEIS provides a dynamic public health surveillance system, emphasizing diseases which are uniquely suited to study in sub-Saharan Africa. The system will allow collection, analysis, and dissemination of data in near real-time.

The USAMRU-K has developed and established a robust infectious disease surveillance program consisting of well-equipped and staffed international surveillance sites, capable central laboratory facilities, a strong educational program, and dedication to infrastructure development within our host nations. The USAMRU-K GEIS surveillance network consists of six sites in Kenya and one site in Uganda. The Kenyan sites are located at the Malindi District Hospital, the Kijabe Medical Centre, the Isiolo District Hospital, the New Nyanza Provincial Hospital, the Alupe Sub-District Hospital, and the Moi Referral and Teaching Hospital. In Uganda, surveillance is performed at the Kalisizo District Hospital in conjunction with the Rakai Project. Each site is staffed with a clinical officer and a laboratory technician whose primary duties are to perform infectious disease surveillance as directed by USAMRU-K. Computer courses are offered to all members of the surveillance staff to ensure competence to perform data entry and basic data analysis. Each site is also provided with the laboratory equipment and supplies required to carry out all of the surveillance functions. Although the majority of laboratory testing is performed at the central laboratory facilities in Nairobi, each site is capable of performing malaria smears and rapid testing for hepatitis B. All sites are equipped with a computer and an Internet connection, to allow real-time transmission of data and communication between field sites and central laboratory facilities. There are three major surveillance activities underway in Kenya and Uganda: active sentinel surveillance for viral hemorrhagic fevers; laboratory-based surveillance for malarial, arboviral, viral hepatitic, rickettsial, or leptospiral etiologies of severe, acute febrile illnesses; and in vitro antimalarial resistance surveillance. The viral hemorrhagic fever and acute febrile illness surveillance projects make use of the tremendous resources available at KEMRI's Centre for Virus Research.

The antimalarial sensitivity protocol assesses parasites taken from 100 smear-positive patients at each site twice per year, as well as 15 per week, every week from the Kalisizo Hospital site. Following the rainy season, each site collects 100 whole blood samples and blood spots from smear-positive patients at their sites and sends the samples to the laboratory in Nairobi, which then cultures the parasites and tests for resistance to 16 commonly used antimalarials.

The influenza surveillance project collects up to five throat swabs per week for viral culture, which is performed at Brooks AFB in the U.S. The diarrheal illness study will make use of the KEMRI Centre for Microbiology Research's facilities in Nairobi. Each surveillance site will provide 100 stool samples twice per year. These will be tested for rotaviral, parasitic, and bacterial etiologies of the diarrheal illness. Those with a bacterial etiology will undergo sensitivity testing against antibiotics in common use. The GEIS program at USAMRU-K is also active in host-nation capacity building, both in personnel assets and in structural development. A teaching program for U.S. medical students and residents has been developed which has been well received by the two students and two residents who have gone through this program. Finally, we are initiating a student attachment program for students completing their laboratory training in Kenya. Twelve students per year will undergo 2 months of training in epidemiology, surveillance techniques, outbreak control, and laboratory identification of epidemic-prone agents such as cholera, viral hemorrhagic fevers, and malaria.

### Summary

The USAMRU-K is the only U.S. DOD infectious disease laboratory in sub-Saharan Africa. It is uniquely positioned to test improved products for the diagnosis, treatment, and prevention of infectious disease threats to deployed service members. It also undertakes surveillance activities to identify and develop response strategies for emerging infections that have the potential to disrupt military readiness. Collaborations with host nation institutions and with regional medical resources are keys to the success of this mission.

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# Research at the Command's Bioinformatics Cell

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*Bioinformatics is just one area the Telemedicine and Advanced Technology Research Center (TATRC) explores in its quest to find leading-edge medical technologies to help the warfighter. The TATRC is a subordinate element of the U.S. Army Medical Research and Materiel Command (USAMRMC) and is charged with managing core research development test and evaluation and congressionally mandated projects in telemedicine and advanced medical technologies. To support its research and development efforts, TATRC maintains a productive mix of partnerships with federal, academic, and commercial organizations. The TATRC also provides short duration, technical support (as directed) to federal and defense agencies; develops, evaluates, and demonstrates new technologies and concepts; and conducts market surveillance with a focus on leveraging emerging technologies in health care and health care support. Ultimately, TATRC's activities strive to make medical care and services more accessible to Soldiers, Sailors, Marines, and Airmen, reduce costs, and enhance the overall quality of military health care.*

## Introduction

Recognizing the need to develop in-house expertise in the quickly growing and rapidly changing fields of bio and medical informatics, the USAMRMC charged its TATRC to establish a bioinformatics cell (BIC). The BIC consists primarily of physical scientists with backgrounds in statistics, computer science, mathematics, and engineering, and has both internal and external missions. Its external mission is to monitor new and emerging technology developments in bioinformatics to enable the identification of new opportunities, publicize Army requirements, influence the course of biotechnology developments, establish strategic alliances and partnerships with industry, academia, and other government agencies, including other Services within the Department of Defense, and to serve as the Command's focal point for coordination of bioinformatics-related Congressional Special Interest (CSI) projects.<sup>1</sup>

The BIC's internal mission is to serve as the USAMRMC advisor for bioinformatics to help align the Command's portfolio and investment strategy with new developments and emerging technologies and to support research efforts that cut across the four major research focus areas of the Command: Military Infectious Diseases, Combat Casualty Care, Military Operational Medicine, and Medical Chemical and Biological Defense. The BIC staff is involved in various activities ranging from organizing bioinformatics workshops to hosting tutorials to performing joint research with the Command's life scientists in both bio and medical informatics. The following sections summarize our research activities in these two research areas.

## Bioinformatics Research

Bioinformatics research at the BIC involves the development of software systems to warehouse, manage, and

analyze genomic and proteomic data. These activities will help us gain insight into gene function and protein function/structure in support of the Command's missions to develop improved assays for threat detection and diagnostics, characterize health effects from exposure to military relevant toxic hazards, and develop medical countermeasures in the form of drugs and prophylactics.

*High Throughput Gene Functional Analysis.* High throughput deoxyribonucleic acid (DNA) microarray technology is being widely exploited by USAMRMC investigators across the four major research focus areas of the Command.<sup>2</sup> In support of these activities, we are collaborating with Wayne State University to extend functional analysis tools, such as Onto-Tools, to support animal models, such as *Caenorhabditis elegans* and rats, being used by our investigators at the Center for Environmental Health Research and the U.S. Army Institute for Surgical Research (USAISR), respectively.<sup>3</sup> These tools allow the automatic translation of lists of genes found to be differentially regulated under given conditions into functional profiles, which permit the characterization of the impact of the condition studied upon various biological processes and pathways.

In collaboration with the U.S. Army Research Institute of Environmental Medicine (USARIEM), we are developing analysis of variance (ANOVA)-based algorithms that permit statistical evaluation of the contribution and significance of different factors to changes in gene expression.<sup>4</sup> Unlike most off-the-shelf statistical analysis packages, which limit the number of repeated measures multiway ANOVA analyses that can be performed at a time, our algorithms have no such restrictions. This allows us to perform time course analyses of all 30,000 genes of prevailing gene arrays within a single computation, where time is the repeated measured factor.

**Management and Analysis of DNA Microarrays.** The BIC is also initiating a new project involving the management and analysis of high throughput DNA microarrays. Our goal is to employ mostly open-source software to warehouse, filter, and analyze DNA microarray studies and associated animal-model physiologic data. Open-source relational database systems will be modified to accommodate specific data requirements and will be integrated with sophisticated open-source and open-development analysis packages, such as Bioconductor.<sup>5</sup> This open-source strategy leverages the work of a large number of contributors world-wide and accommodates the necessity of frequent software updates for this emerging and rapidly changing technology.

**Design of Biosensors for Threat Diagnosis.** We are developing bioinformatics-based tools to help guide the design of gene chips (assays) to detect and identify human exposure to infectious agents (Figure 1) in collaboration with life-science colleagues from the Command's Research Institute of Infectious Diseases. Our current approach uses existing software that searches for sequence similarity to identify fragments of a pathogen DNA or "fingerprints" that are unique to that pathogen when compared across all known sequenced genomes. Due to the large dimensionality of the search space ( $10^6$ - $10^9$  base-pairs/pathogen and ~140,000 organisms) this computation for a single pathogen may take several days in a serial 2.4 GHz machine. Hence, future efforts involve the scaling of these algorithms to a high-performance computing platform and the development of new algorithms that are designed from their onset to identify sequence *dissimilarity* (which is our interest) rather than *similarity*.

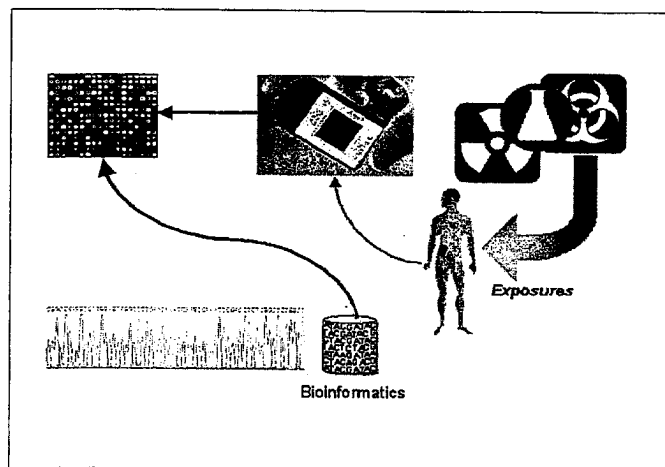


Fig 1. Bioinformatics-based software to help guide the design of diagnostic assays ("gene chips") to detect and identify human exposure to infectious agents.

**Characterization of Protein Structure and Function.** Another challenging bioinformatics project involves the development of algorithms for the identification of protein

markers that can be used to characterize protein function and structure. These algorithms will form the basis for methods to identify infectious threat agents that have been genetically engineered to foil conventional sequence-based detection approaches, to identify markers of molecules that render microorganisms resistant to currently available antibiotics, and to characterize protein function. This last functionality will help analyze the large percent of amino acid sequences identified by present-day microbial genome projects that have no identifiable structures, as assessed by standard methods, thus requiring prolonged and expensive laboratory efforts to characterize their functions.

In collaboration with Argonne National Laboratory, a multi-disciplinary Department of Energy laboratory, we have developed machine-learning support vector machine algorithms that combine protein sequence information, and more recently, protein 3-dimensional structure information to classify proteins based on their function.<sup>6</sup> One of the key features of these algorithms is the ability to sift through various amino acid substitutions (in this study, sequences with up to 40% of amino acid substitutions were observed) to identify which site substitutions are critical in changes in protein function.

We are also initiating a new project focused on characterizing the structure and function of proteins that exhibit low sequence similarity (<25%) when compared with sequences of known structure and function in existing databases. In this project, new algorithmic search strategies will be developed and implemented with an objective of characterizing 50% of the present-day microbial genome sequences that consist of "hypothetical" proteins of unknown function, as they have insufficient identity to well-characterized proteins. A case in point of a microorganism of military relevance is the recently sequenced malaria parasite, *Plasmodium falciparum*, consisting of ~5300 regions that encode into proteins (open reading frames) of which 60% have unknown – or perhaps, unrecognizable – function.

## Medical Informatics Research

The BIC's research efforts in medical informatics involve the development of computer systems for management and analysis of physiologic data and the development of predictive and decision support algorithms for the prevention of disease and the management of nonbattle and combat casualty injuries.

**Data Management and Analysis System.** Our physiology analysis system (PAS) is built on a combination of proven computational platforms and is easily accessible through the web. The PAS is designed to provide a flexible solution to warehouse, manage, and mine large volumes of time-series

physiologic data, such as waveforms for electrocardiograms, oxygen saturation, and respiration, from multiple studies in a central location. The PAS also provides analytical tools for use

by scientists for data analysis, including data query, visualization, and cleansing as well as tools for feature selection and model development (Figure 2).

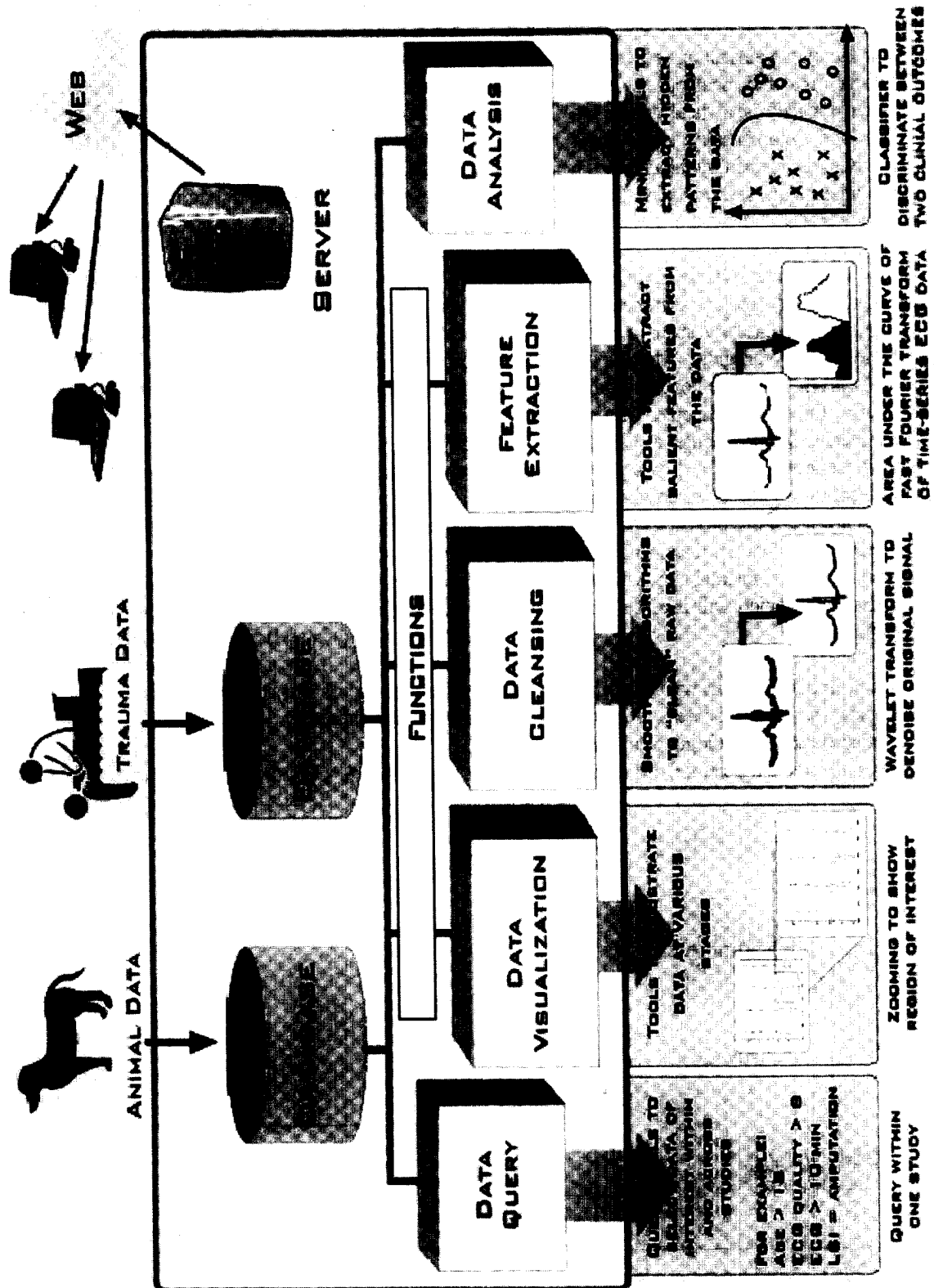


Fig 2. The PAS provides a web-based, flexible platform to warehouse, manage, and mine multiple studies involving large amounts of time-series physiologic data in a central location.

The innovative concept of PAS relates to its architecture where both the data and the analysis tools reside at the server while offering – through a web browser – a feature-rich, workstation-like environment that researchers require to perform sophisticated data mining. This architecture eliminates the need to download tools and data from the server to the user's computer and avoids the often-painstaking process of installing the downloaded tools into the desktop. It allows rapid incorporation of user-provided analytical tools into PAS's library of functions and automatically keeps track of the sequence of analysis steps performed by the user and generates derivative data only when requested, reducing the amount of data the system has to manage.

*Casualty Triage Algorithms.* We are mining pre-hospital trauma data to identify physiologic parameters that are diagnostic and prognostic for casualty status and to develop triage algorithms for the Warfighter Physiologic Status Monitoring (WPSM) system.<sup>7</sup> Our pre-hospital civilian trauma data is collected during life flight helicopter transport to the University of Texas Health Science Center at Houston, a CSI partner. The data is collected with a Propaq system and associated hardware/software interface configured by the USAISR. The chief objective of this project is the identification of key physiologic parameters that are diagnostic or predictive of some clinical outcome, such as internal hemorrhage or a need for a lifesaving intervention, which will then be employed to develop triage algorithms.

A second project, in collaboration with a small business, centers on developing a statistics-based decision-support algorithm to interpret streaming physiologic data (for example, heart rate, respiratory rate, skin temperature) from a suite of

wearable biosensors to remotely and automatically assess the physiologic status (life sign) of a wounded Soldier in the battlefield.<sup>8</sup> The algorithm incorporates, as part of the decision-making process, both clinical uncertainty (for example, potential contradictory evidence, the number of available physiologic sensors, and temporal evolution of the symptoms from injury onset) and data imprecision (for example, missing, degraded, or corrupted data due to sensor faults, data transmission failures, and sensor dislodgment). The algorithm, based on Bayesian belief networks and related Decision Theory technologies, has a probabilistic foundation and provides the mathematical formalism whereby medical judgment may be expressed as the degree of belief in an outcome given a set of observations.

*Physiology-Based Predictive Algorithms.* In collaboration with USARIEM and in support of the WPSM, we are developing hybrid computer-based algorithms to predict the physiologic state of individual Soldiers.<sup>9</sup> For instance, as illustrated in Figure 3, these algorithms may take as inputs a multitude of anthropometric, environmental, and on-line physiology measurements to infer, in real time, an individual's level of fatigue or propensity to become a heat casualty. The hybrid algorithms combine mechanistic first-principles-based models, such as the macroscopic conservation of mass and energy, with data-driven algorithms in the form of artificial neural networks. This combined modeling approach yields Soldier-specific predictive models that maximize the use of prior physiology knowledge and, through information extracted from on-line measurements, complements our partial understanding of physiologic phenomena and accounts for inter-person variability.

*Automatic Control of Resuscitation Fluids.* In collab-

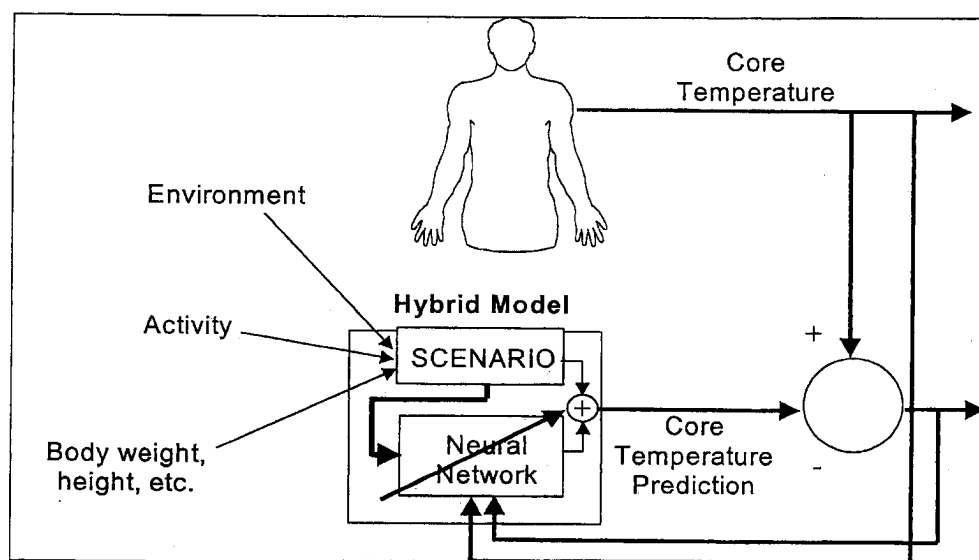


Fig 3. Hybrid models combining first-principles-based physiologic models and data-driven models for predicting the physiologic state of an individual Soldier.

oration with researchers at the Walter Reed Army Institute of Research (WRAIR), we are modeling blood pressure responses in pigs to infusion of various fluids during resuscitation after severe blood loss. Our objective is to use the models to evaluate candidate algorithms to automate resuscitation of the pigs, and ultimately humans, via control of an infusion pump. Our pressure/volume models are based on autoregressive moving average and autoregressive integrating moving average algorithms. Pressure/volume relationships during resuscitation are erratic because of numerous sources of variability, such as differences in pig-to-pig physiology, the blood pressure against which the infusion is occurring, the rate of infusion, the total interval of infusion, and the viscosity and distribution characteristics of the different infusion fluids. Because of this variability, we are investigating a range of potential infusion pump control algorithms, including proportional-integrating-differential and its variations, fuzzy logic, and self-tuning. The ultimate goal of this project is to integrate the selected controller into a computer assisted resuscitation algorithm (CARA), which is a critical component of WRAIR's Critical Care System for Trauma and Transport platform (CSTAT).<sup>10</sup> The CSTAT is an enhanced litter that incorporates significant patient monitoring and, as is exemplified by CARA, computer assisted patient care capabilities.

## Conclusion

The BIC is a USAMRMC resource that supports bio and medical informatics activities that cut across the four major research focus areas of the Command: Military Infectious Diseases, Combat Casualty Care, Military Operational Medicine, and Medical Chemical and Biological Defense. The BIC performs inter-disciplinary research that covers a wide range of technology areas in collaboration with multiple life-science investigators throughout the Command's laboratories. As we move forward, we plan to leverage, to the maximum extent possible, the BIC's bioinformatics-related CSI projects with these internal activities.

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# Hu BChE: A Bioscavenger for Protection Against Organophosphate Chemical Warfare Agents

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*Several studies over the last two decades have demonstrated that the exogenous administration of human serum butyrylcholinesterase (Hu BChE) can be successfully used as a safe and efficacious prophylactic treatment to prevent poisoning by organophosphorus (OP) compounds. A dose of 200 mg of Hu BChE is envisioned as a prophylactic treatment in humans that can protect from exposure of up to 2 x LD<sub>50</sub> of soman (GD). In addition to its use as a prophylactic for a variety of wartime scenarios, including covert actions, it also has potential use for first responders (civilians) reacting to terrorist nerve gas release. In summary, Hu BChE purified from Cohn fraction IV exhibits a remarkable shelf life, displays long-lasting stability in the circulation of rodents and nonhuman primates, and is devoid of any toxic side effects. These results provide convincing data for the continued development of Hu BChE as a bioscavenger that can protect humans against all OP nerve agents.*

## Introduction

Although current antidotal regimens for OP poisoning are effective in preventing lethality of animals from OP poisoning, they do not prevent post-exposure incapacitation, convulsions, performance deficits or in many cases, permanent brain damage.<sup>1-3</sup> These problems stimulated the development of enzyme bioscavengers as a pretreatment to sequester highly toxic OPs before they reach their physiological targets and prevent the in vivo toxicity of OPs and post-exposure incapacitation.<sup>3</sup> Among the enzymes examined as potential scavengers of highly toxic OP nerve agents, significant advances have been made using cholinesterases (ChEs). Of the ChEs evaluated so far, Hu BChE has several advantages as an exogenously administered prophylactic for human use.<sup>4</sup> First, it reacts rapidly with all highly toxic OPs, offering a broad range of protection for nerve agents including GD, sarin, tabun, and methyl, O-ethylphosphonyl-adduct (VX). Second, it possesses a very long retention time in human circulation and is readily absorbed from sites of injection. Third, since the enzyme is from a human source, it should not produce any adverse immunological responses upon repeated administration into humans. A dose of 200 mg of Hu BChE is envisioned as a prophylactic treatment in humans that can protect from exposure of up to 2 x LD<sub>50</sub> of GD.<sup>4</sup>

The foremost requirement to advance Hu BChE as a

bioscavenger for human use was to obtain sufficient amounts of purified enzyme for conducting animal and clinical studies. A richer source of Hu BChE was identified as Cohn Fraction IV-4 paste, which contains ~150 mg of enzyme per kg. A procedure for the large-scale purification of Hu BChE was developed, which yielded 6 g of purified enzyme from 120 kg of Cohn Fraction IV-4 paste. The objective of the current effort was to provide pre-clinical pharmacological information for conducting phase I clinical trials of Hu BChE in humans. However, prior to the first-dose-in-man studies, the safety of an experimental drug must be assessed in two animal models to identify or characterize any secondary unwanted pharmacological or toxicological effects, which could influence organ functions in humans. In addition, results of pharmacokinetic studies and in vitro stability of the enzyme will provide valuable guidelines for its dose design and storage shelf life. Therefore, we investigated the pharmacokinetics as well as safety and toxicity of purified Hu BChE in mice and guinea pigs. Blood was sampled at various time intervals to characterize the pharmacokinetics of Hu BChE in mice and guinea pigs following i.p. or i.m. administrations. The safety and toxicity of Hu BChE was measured by general observation, serum chemistry, and hematology. Animals were euthanized at the end of 2 weeks and tissues were examined grossly or microscopically for possible toxic effects. The stability of the enzyme stored at 4°, 25°, 37°, and 45°C was determined in lyophilized form. The effect of storage at -20°C on circulatory

stability was also determined by measuring the mean residence time (MRT) of enzyme in mice. The efficacy of the enzyme against GD and VX was evaluated in guinea pigs. The immunological consequences of administration of purified Hu BChE into mice were also assessed, following two injections, administered 4 weeks apart. These initial results provide convincing data that Hu BChE is a safe and effective bioscavenger that can protect humans against all OP nerve agents.

## Methods

Research was conducted under a protocol approved by the WRAIR IACUC, in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals, experiments involving animals, and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals*.

### Pharmacokinetics and Bioavailability of Hu BChE

**Mice.** Thirty-six CD-1 mice (8 weeks old, equal number of male and female, weight 25-30 g) were divided into 6 groups ( $n=6$ ). Animals in each group were injected with Hu BChE (0.1, 1, or 3 mg) by i.m. or i.p. injections. Two extra groups of animals injected with saline only by either i.m. or i.p. injection, served as controls. Following enzyme administration, 10  $\mu$ L of blood was drawn from the tail vein at various time intervals and diluted 20 times with water for the determination of blood BChE activity.<sup>5</sup> The following pharmacokinetic parameters were determined from the time course curve of blood BChE concentration: MRT, maximal concentration ( $C_{max}$ ), time to reach the maximal concentration ( $T_{max}$ ), elimination half-life ( $T_{1/2}$ ), and area under the plasma concentration time curve extrapolated to infinity (AUC), using a Windows-based program for noncompartmental analysis of pharmacokinetic data.<sup>6</sup>

**Guinea Pigs.** Hu BChE (60 mg/kg) was administered to guinea pigs (equal number of male and female;  $n=6$ ) by a single i.p. or i.m. injection. Blood samples were taken at various time points for up to 14 days for the measurement of blood BChE activity and the determination of pharmacokinetic parameters as described above.

### Safety and Toxicity of Hu BChE

Animals were observed for any abnormal physiological or behavioral signs for 2 weeks after enzyme administration. After 14 days, the animals were euthanized and blood was collected for determining hematology and serum chemistry parameters. Following blood collection, a complete necropsy was performed and a full set of tissues, including brain, heart, lung,

liver, intestine, kidney, eye, spleen, and muscle injection sites, were examined for any gross or histological changes.

### In Vitro and In Vivo Stability of Hu BChE

Aliquots of enzyme (1 mg) were stored in lyophilized form at 4°, 25°, 37°, or 45°C. Samples were resuspended in 1 ml of 50 mM sodium phosphate buffer, pH 8.0 at various time intervals and assayed for BChE activity as described.<sup>5</sup> In vivo circulatory stability of the enzyme was determined by measuring the pharmacokinetic profile of the enzyme (stored at -20°C for various time periods) following i.m. administration into mice as described above.

### Efficacy Studies of Hu BChE in Guinea Pigs

Guinea pigs ( $n=10$ ) were administered Hu BChE, i.m., in sufficient quantity to neutralize an 8 x LD<sub>50</sub> challenge of GD (1 x LD<sub>50</sub> = 30  $\mu$ g/kg sc) or VX (1 x LD<sub>50</sub> = 9  $\mu$ g/kg sc) based on theoretical calculations. At 19 ( $\pm$  1.0) h post administration, a blood sample was taken via toe clip and the whole blood BChE concentration was determined. A molar amount of GD or VX equivalent to 1.5 x LD<sub>50</sub> was given sc and the animals were observed for signs of intoxication for 90 minutes. At the end of that period, a second blood sample was taken and the whole blood BChE concentration redetermined. On the basis of BChE activity in circulation, the animals were administered another 2 x LD<sub>50</sub> of GD or VX sc. Again the animals were observed for signs of intoxication for 90 minutes and if none were observed, the process was repeated one more time. Ninety minutes after the third dose of GD or VX, a final blood sample was taken and analyzed for whole blood BChE concentration. Surviving animals were held for 7 days at which time one-half the surviving population was randomly euthanized for histopathology studies.

### Immunologic Consequences of Exposing Mice to Hu BChE

Mice (CD-1) were injected i.m. with 100 U of purified Hu BChE or mouse (Mo) BChE (purified from the plasma of CD-1 mice), followed by a second i.m. injection of 100 U 4 weeks later. Blood samples were withdrawn immediately before and multiple times after injection to monitor BChE activity and antibody levels.<sup>5,7,8</sup> The presence of anti-Hu BChE or anti-Mo BChE antibodies was followed by ELISA, using 0.2 U of Hu BChE or Mo BChE per well as the plate-coating antigen, respectively.<sup>8</sup> Mouse antibody binding to Hu BChE was detected with peroxidase-labeled goat antibody to mouse IgG using ABTS substrate. Standard curves using purified mouse IgG were run with each assay to allow quantification of antibody response.

## Results and Discussion

**Pharmacokinetics of Hu BChE.** Time courses of Hu BChE administered by two different routes in mice, are shown in Figure 1 and the pharmacokinetic parameters are shown in Table 1. Time courses of Hu BChE administered by i.m. and i.p. injections in guinea pigs are shown in Figure 2 and the pharmacokinetic parameters are shown in Table 2. Purified Hu BChE exhibited circulatory stability profiles similar to those observed previously for enzyme purified from human plasma in rats and mice, guinea pigs, and rhesus monkeys.<sup>9-11</sup> Mice that administered 70-2100 U of Hu BChE by i.p. injection showed a rapid increase in BChE activity, which reached peak levels at ~10 h. On the other hand, when the same doses of enzyme were delivered by i.m. injections, peak levels of activity were attained at ~24 h. Regardless of the dose and route of administration, the enzyme displayed a MRT of 45-51 h. Similar circulatory profiles of Hu BChE were observed for both i.p. and i.m. routes of administrations in guinea pigs, with MRT values that were almost twice those observed in mice.

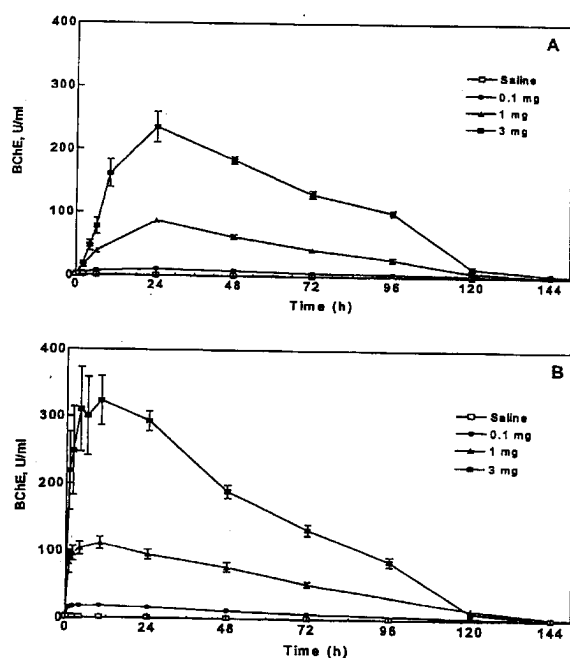


Fig 1. Average enzyme levels in blood of mice following i.m. (panel A) and i.p. (panel B) injections of various doses of Hu BChE.

Parameters	0.1 mg		1 mg		3 mg	
	i.p.	i.m.	i.p.	i.m.	i.p.	i.m.
MRT (h)	46.7 ± 2.1	50.2 ± 3.2	45.5 ± 2.3	47.3 ± 3.2	42.2 ± 2.5	51.0 ± 2.3
T <sub>1/2</sub> (h)	18.9 ± 0.8	16.3 ± 0.4	13.6 ± 0.9	11.7 ± 0.8	10.9 ± 1.2	15.6 ± 1.3
T <sub>max</sub> (h)	10 ± 3	24 ± 0	14 ± 4	24 ± 0	14 ± 5	24 ± 0
C <sub>max</sub> (U/ml)	17.9 ± 1.4	10.1 ± 0.5	110.7 ± 13.6	86.4 ± 5	363.9 ± 51.2	225.0 ± 23.2
AUC	1,146 ± 66	754 ± 44	7,359 ± 1,135	5,718 ± 356	20,279 ± 1,428	16,162 ± 1,258

Table 1. Pharmacokinetic Parameters of Hu BChE in Mice

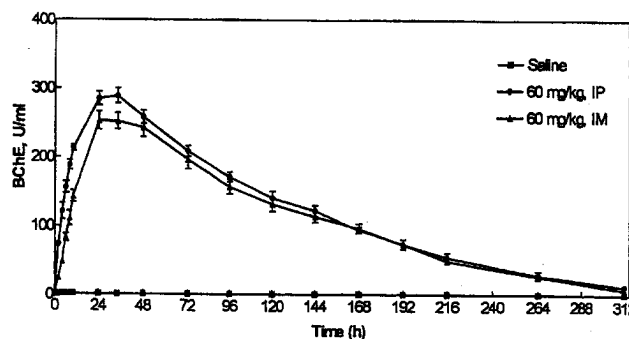


Fig 2. Time course of Hu BChE activity in blood of guinea pigs following i.p. and i.m. administrations.

Parameters	Hu BChE, i.m.	Hu BChE, i.p.
MRT (h)	110 ± 4	109 ± 6
T <sub>1/2</sub> (h)	61.7 ± 3.8	63.1 ± 7.2
T <sub>max</sub> (h)	27 ± 2	30 ± 2
C <sub>max</sub> (U/ml)	258 ± 12	293 ± 12.4
AUC	35,196 ± 2,084	39,163 ± 1,714

Table 2. Pharmacokinetic Parameters of Hu BChE in Guinea Pigs

## Safety and Toxicity of Hu BChE

Mice with circulating levels of BChE as high as 300 U/ml, did not display any signs of clinical toxicity. Animals were euthanized after 2 weeks post Hu BChE injections and blood samples were examined for hematology (Table 3) and serum chemistry parameters (Table 4). Results of necropsy performed on animals, together with the examination of hematology and serum chemistry parameters, did not reveal any clinical signs of pathology following the administration of large doses of Hu BChE. Similarly, guinea pigs administered 60 mg/kg of Hu BChE were euthanized after 14 days and blood samples were evaluated for serum chemistry and hematology parameters. As with mice, no changes were observed in histopathology or hematology (Table 5) or serum chemistry parameters (Table 6).

Parameters	Saline		0.1 mg		1 mg		3 mg	
	i.m.	i.p.	i.m.	i.p.	i.m.	i.p.	i.m.	i.p.
WBC ( $10^3/\text{mm}^3$ )	$3.1 \pm 0.5$	$3.3 \pm 0.8$	$6.0 \pm 1.0$	$5.0 \pm 0.9$	$3.7 \pm 0.5$	$4.0 \pm 0.7$	$4.6 \pm 0.6$	$5.0 \pm 0.4$
RBC ( $10^6/\text{mm}^3$ )	$7.44 \pm 0.16$	$6.63 \pm 0.43$	$7.71 \pm 0.24$	$7.16 \pm 0.19$	$7.21 \pm 0.15$	$6.60 \pm 0.52$	$7.91 \pm 0.29$	$8.51 \pm 0.14$
HGB (g/dl)	$12.0 \pm 0.2$	$10.9 \pm 0.5$	$12.5 \pm 0.3$	$11.6 \pm 0.2$	$11.8 \pm 0.3$	$10.4 \pm 0.6$	$13.1 \pm 0.2$	$13.8 \pm 0.3$
HCT (%)	$34.2 \pm 0.6$	$31.5 \pm 1.7$	$35.7 \pm 0.8$	$33.7 \pm 0.6$	$34.6 \pm 0.9$	$30.8 \pm 1.9$	$36.1 \pm 0.8$	$37.9 \pm 1.0$
MCV ( $\mu\text{m}^3$ )	$46 \pm 0$	$48 \pm 1$	$46 \pm 1$	$47 \pm 0$	$48 \pm 1$	$47 \pm 1$	$46 \pm 2$	$46 \pm 2$
MCH (pg)	$16.2 \pm 0.2$	$16.5 \pm 0.3$	$16.2 \pm 0.2$	$16.3 \pm 0.2$	$16.3 \pm 0.2$	$15.8 \pm 0.3$	$16.6 \pm 0.7$	$16.6 \pm 0.5$
MCHC (g/dl)	$35.1 \pm 0.2$	$34.7 \pm 0.4$	$34.9 \pm 0.2$	$34.5 \pm 0.2$	$34.0 \pm 0.1$	$33.7 \pm 0.3$	$36.4 \pm 0.1$	$36.6 \pm 0.3$
RDW (%)	$12.4 \pm 0.2$	$13.2 \pm 0.2$	$12.7 \pm 0.2$	$12.6 \pm 0.2$	$12.5 \pm 0.1$	$13.3 \pm 0.2$	$14.8 \pm 0.5$	$14.0 \pm 0.6$
PLT ( $10^3/\text{mm}^3$ )	$718 \pm 47$	$603 \pm 56$	$739 \pm 48$	$638 \pm 48$	$637 \pm 55$	$640 \pm 42$	$745 \pm 43$	$605 \pm 150$
MPV ( $\mu\text{m}^3$ )	$5.4 \pm 0.1$	$5.5 \pm 0.1$	$5.9 \pm 0.1$	$5.3 \pm 0.1$	$5.2 \pm 0.1$	$5.5 \pm 0.1$	$5.6 \pm 0.2$	$6.0 \pm 0.3$

Values are MEAN $\pm$ SE. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red blood cell distribution width; PLT: platelets; MPV: mean platelet volume.

Table 3. Hematology Parameters in Mice Injected with Various Doses of Hu BChE

Parameters	Vehicle		0.1 mg		1 mg		3 mg	
	i.m.	i.p.	i.m.	i.p.	i.m.	i.p.	i.m.	i.p.
Glucose (mg/dl)	$268 \pm 18$	$284 \pm 17$		$275 \pm 24$	$232 \pm 13$	$296 \pm 11$	$217 \pm 24$	$162 \pm 18$
UREA Nitrogen (mg/d)	$25 \pm 2$	$26 \pm 2$	$26 \pm 2$	$24 \pm 2$	$23 \pm 1$	$23 \pm 1$	$22 \pm 3$	$20 \pm 1$
Creatinine (mg/dl)	$0.2 \pm 0.0$	$0.2 \pm 0.0$	$0.2 \pm 0.0$	$0.2 \pm 0.0$	$0.2 \pm 0.0$	$0.2 \pm 0.0$	$0.2 \pm 0.0$	$0.2 \pm 0.0$
Sodium (mmol/l)		$140 \pm 1$		$141 \pm 1$	$147 \pm 1$	$144 \pm 1$	$151 \pm 1$	$151 \pm 1$
Potassium (mmol/l)		$5.9 \pm 0.5$		$6.1 \pm 0.8$	$5.8 \pm 0.3$	$5.3 \pm 0.6$	$6.4 \pm 0.3$	$5.4 \pm 0.2$
Chloride (mmol/l)		$108 \pm 1$		$107 \pm 1$	$112 \pm 1$	$110 \pm 1$	$109 \pm 1$	$108 \pm 1$
Bicarbonate (mmol/l)	$26 \pm 1$	$25 \pm 1$		$26 \pm 1$	$21 \pm 2$	$23 \pm 1$	$20 \pm 2$	$20 \pm 1$
Calcium (mg/dl)	$8.5 \pm 0.1$	$8.1 \pm 0.2$		$8.2 \pm 0.1$	$9.8 \pm 0.9$	$8.7 \pm 0.1$	$9.5 \pm 0.2$	$9.1 \pm 0.2$
Phosphorus (mg/dl)	$7.0 \pm 0.3$	$6.9 \pm 0.5$	$6.7 \pm 0.4$	$6.7 \pm 0.4$	$6.7 \pm 0.5$	$6.2 \pm 0.3$	$10.1 \pm 0.4$	$8.9 \pm 0.5$
Cholesterol (mg/dl)	$115 \pm 12$	$87 \pm 8$		$110 \pm 10$	$104 \pm 7$	$97 \pm 8$	$142 \pm 13$	$100 \pm 7$
Triglycerides (mg/dl)	$84 \pm 7$	$114 \pm 16$		$97 \pm 9$	$108 \pm 15$	$94 \pm 9$	$125 \pm 16$	$113 \pm 18$
Total Protein (g/dl)	$4.4 \pm 0.0$	$4.3 \pm 0.1$	$4.4 \pm 0.1$	$4.4 \pm 0.1$	$4.8 \pm 0.1$	$4.6 \pm 0.1$	$5.3 \pm 0.1$	$5.5 \pm 0.2$
Albumin (g/dl)	$1.8 \pm 0.0$	$1.7 \pm 0.1$	$1.8 \pm 0.1$	$1.8 \pm 0.1$	$2.0 \pm 0.1$	$1.9 \pm 0.0$	$2.5 \pm 0.1$	$2.6 \pm 0.3$
AST (U/l)	$80 \pm 9$	$132 \pm 21$	$107 \pm 18$	$190 \pm 53$	$103 \pm 32$	$141 \pm 36$	$91 \pm 9$	$293 \pm 142$
ALT (U/l)	$41 \pm 9$		$45 \pm 6$	$66 \pm 20$	$64 \pm 12$	$58 \pm 8$	$32 \pm 8$	$60 \pm 5$
ALKP (U/l)	$119 \pm 10$	$61 \pm 5$	$95 \pm 17$	$67 \pm 6$	$106 \pm 13$	$68 \pm 9$	$126 \pm 21$	$112 \pm 101$
GGT (U/l)	$13 \pm 1$	$9 \pm 1$	$13 \pm 1$	$11 \pm 0$	$22 \pm 7$	$11 \pm 0$	$8 \pm 1$	$23 \pm 265$
Total BILI (U/l)	$0.6 \pm 0.1$	$0.6 \pm 0.1$		$0.5 \pm 0.1$	$0.8 \pm 0.2$	$0.3 \pm 0.1$	$0.7 \pm 0.1$	$0.7 \pm 0.3$

Values are MEAN $\pm$ SE. ALKP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; MCH: mean corpuscular hemoglobin.

Table 4. Serum Chemistry Parameters in Mice Injected with Various Doses of Hu BChE

Hematology Parameters	Saline	Hu BChE, 60 mg/kg i.m.	Hu BChE, 60 mg/kg i.p.
WBC ( $10^3/\text{mm}^3$ )	$4.0 \pm 0.3$	$4.2 \pm 0.5$	$4.5 \pm 0.5$
RBC ( $10^6/\text{mm}^3$ )	$5.00 \pm 0.10$	$5.49 \pm 0.13$	$5.46 \pm 0.07$
HGB (g/dl)	$13.8 \pm 0.3$	$15.3 \pm 0.4$	$15.1 \pm 0.2$
HCT (%)	$40.5 \pm 0.8$	$46.0 \pm 1.4$	$44.7 \pm 0.6$
MCV ( $\mu\text{m}^3$ )	$81 \pm 1$	$84 \pm 1$	$82 \pm 0$
MCH (pg)	$27.7 \pm 0.4$	$27.8 \pm 0.5$	$27.6 \pm 0.2$
MCHC (g/dl)	$34.2 \pm 0.1$	$33.2 \pm 0.1$	$33.8 \pm 0.2$
RDW (%)	$9.2 \pm 0.1$	$9.1 \pm 0.2$	$9.3 \pm 0.2$
PLT ( $10^3/\text{mm}^3$ )	$294 \pm 55$	$217 \pm 26$	$310 \pm 55$
MPV ( $\mu\text{m}^3$ )	$7.8 \pm 0.3$	$7.9 \pm 0.2$	$7.8 \pm 0.4$

Values are MEAN  $\pm$  SE. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red blood cell distribution width; PLT: platelets; MPV: mean platelet volume.

Table 5. Hematology Parameters in Guinea Pigs Following Administration of Hu BChE

Serum Chemistry Parameters	Saline	Hu BChE, 60 mg/kg i.m.	Hu BChE, 60mg/kg i.p.
UREA Nitrogen (mg/dl)	$16 \pm 1$	$15 \pm 1$	$15 \pm 1$
Creatinine (mg/dl)	$0.4 \pm 0.0$	$0.5 \pm 0.0$	$0.4 \pm 0.0$
Sodium (mmol/l)	$136 \pm 1$	$146 \pm 4$	$134 \pm 1$
Chloride (mmol/l)	$101 \pm 2$	$106 \pm 3$	$101 \pm 1$
Bicarbonate (mmol/l)	$24 \pm 2$	$23 \pm 3$	$22 \pm 3$
Calcium (mg/dl)	$10.5 \pm 0.5$	$10.9 \pm 0.6$	$10.3 \pm 0.5$
Phosphorus (mg/dl)	$9.0 \pm 0.4$	$10.1 \pm 2.0$	$7.8 \pm 1.1$
Cholesterol (mg/dl)	$56 \pm 5$	$52 \pm 8$	$51 \pm 3$
Triglycerides (mg/dl)	$116 \pm 27$	$80 \pm 19$	$85 \pm 10$
Total Protein (g/dl)	$4.3 \pm 0.3$	$4.6 \pm 0.2$	$4.5 \pm 0.1$
Albumin (g/dl)	$2.0 \pm 0.2$	$2.1 \pm 0.2$	$1.9 \pm 0.1$
AST (U/l)	$253 \pm 94$	$99 \pm 28$	$154 \pm 69$
ALT (U/l)	$103 \pm 33$	$48 \pm 3$	$53 \pm 10$
LDH (U/l)	$1662 \pm 298$	$1068 \pm 53$	$1292 \pm 115$
CK (U/l)	$310 \pm 29$	$403 \pm 77$	$320 \pm 72$
ALKP (U/l)	$107 \pm 9$	$132 \pm 4$	$117 \pm 5$
GGT (U/l)	$39 \pm 7$	$45 \pm 5$	$61 \pm 9$
Total BILI (mg/dl)	$0.6 \pm 0.1$	$0.5 \pm 0.1$	$0.5 \pm 0.0$

Values are MEAN  $\pm$  SE. ALKP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CK: creatine kinase; GGT: Gamma-glutamyltranspeptidase; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin.

Table 6. Serum Chemistry Parameters in Guinea Pigs following Administration of Hu BChE

## In Vitro and In Vivo Stability of Hu BChE

The thermal stability of purified Hu BChE stored in lyophilized form, at various temperatures, is shown in Figure 3. The enzyme activity was stable when stored in lyophilized form at 4°, 25°, 37°, or 45°C to date (2 years). The circulatory (in vivo) stability of enzyme stored in lyophilized form at -20°C, was evaluated by measuring pharmacokinetic parameters in mice. As shown in Table 7, the pharmacokinetic properties of the enzyme were not affected upon storage at -20°C to date (2 years).

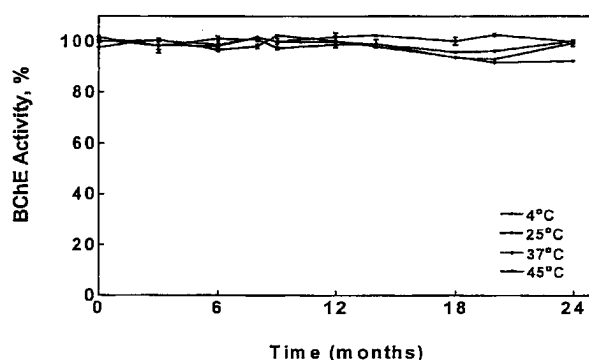


Fig 3. Thermal stability of Hu BChE stored at various temperatures, in lyophilized form.

Parameters	Time of storage at -20°C (months)			
	3	10	17	25
MRT (h)	50.2 ± 3.2	55.2 ± 0.9	50.5 ± 1.4	49.3 ± 0.8
T <sub>1/2</sub> (h)	16.3 ± 0.4	17.9 ± 0.5	24.0 ± 2.4	15.9 ± 0.1
T <sub>max</sub> (h)	24	24	24	24
C <sub>max</sub> (U/ml)	10.1 ± 0.5	11.6 ± 0.4	17.7 ± 0.6	20.6 ± 0.8
AUC	754 ± 44	806 ± 25	1216 ± 35	1411 ± 20

Table 7. In Vivo Stability of Hu BChE in Mice

## Efficacy Studies of Hu BChE in Guinea Pigs

Animals were pretreated with Hu BChE and 18–20 h later they were challenged with either GD or VX. The challenge design allowed for multiple challenges of experimental animals with lethal amounts of GD or VX until a total 5–6 x LD<sub>50</sub> dose was given. In case of GD challenge, all animals (n=10) survived with no observable signs (Table 8). At necropsy, either 7 days (n=5) or 14 days (n=5) post GD challenge, all organs appeared normal and no abnormal histopathology was observed. When animals were challenged with VX (n=9) under a similar paradigm, all animals survived the first and second challenge doses of VX, for a total dose of 5 x LD<sub>50</sub>, with no observable signs of intoxication (Table 8).

Agent	Cumulative Dose (LD <sub>50</sub> )	Impairment	Recovery
GD	5.5	N/A	Immediate
VX	5.0	N/A	Immediate

Table 8. Protection of Guinea Pigs Against Organophosphate Nerve Agent Poisoning by Hu BChE

## Immunologic Consequences of Exposing Mice to Hu BChE

The exogenous administration of plasma-derived ChEs in both rodent and nonhuman primate models has been successfully used as a safe and efficacious prophylactic treatment to prevent poisoning by OP compounds.<sup>12</sup> In these studies, the enzyme was administered by a single injection. However, multiple prophylactic treatments aimed at maintaining long-lasting protective levels of circulating enzyme may be needed to counteract the toxicity of multiple exposures to OPs. Therefore, we examined the consequences of repeated injections of Hu BChE and Mo BChE in mice following two i.m. injections of ~100 U (0.15 mg) on day 1 and on day 28, respectively. This dose is also similar to that envisaged for use in humans (3 mg/kg).<sup>4</sup> The effects of two heterologous (Hu BChE) and homologous (Mo BChE) injections were monitored by following blood BChE (Figure 4A) and anti-BChE IgG (Figure 4B) levels. The pharmacokinetic parameters are shown in Table 9. As observed in most previous studies, the rate of clearance of heterologous Hu BChE and homologous Mo BChE appears to follow an exponential decay equation. However, the clearance of homologous Mo BChE activity following the first injection occurred slowly (MRT = 73 ± 3 h), compared to the heterologous Hu BChE injection (MRT = 48 ± 2 h). As expected, the second injection of 100 U of Hu BChE cleared much faster from the circulation of mice compared to the first injection (MRT = 26 ± 1 h). The second injection of homologous Mo BChE on the other hand, attained a peak enzyme level that was similar to that observed following the first injection, and a similar MRT of 79 ± 6 h.

As expected, circulating anti-Hu BChE IgG could be detected 5 days following the first Hu BChE injection, which increased dramatically after the second injection. No significant antibody response was detected following either of the two homologous BChE injections. The absence of any antibody responses following either injection in a homologous system, are in agreement with the long retention times and the absence of significant adverse effects following administration of homologous macaque BChE into macaques.<sup>8</sup> The observation that the second injection of Mo BChE resulted in a pharmacokinetic profile that was similar to that of the first

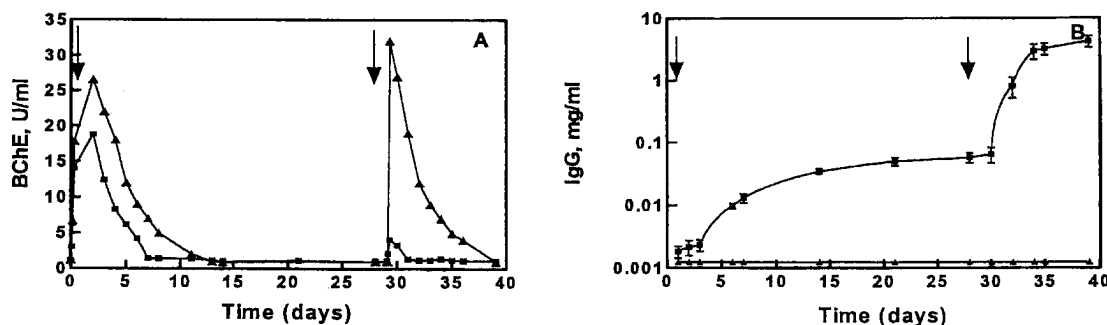


Fig 4. (A) Time courses of Hu BChE (■) and Mo BChE (▲) in blood of mice following two injections of purified Hu BChE and Mo BChE, respectively; (B) Antibody levels in sera of mice following two injections of purified Hu BChE (■) and Mo BChE (▲). The arrows indicate time of first and second injections.

Parameters	First Injection		Second Injection	
	Hu BChE	Mo BChE	Hu BChE	Mo BChE
MRT (h)	48 ± 2	73 ± 3	26 ± 1	79 ± 6
T <sub>1/2</sub> (h)	18 ± 4	22 ± 2	10 ± 2	32 ± 2
T <sub>max</sub> (h)	24	24	24	24
C <sub>max</sub> (U/ml)	19 ± 3	25 ± 3	5 ± 1	31 ± 2
AUC	1301 ± 217	2504 ± 239	165 ± 43	3071 ± 194

Table 9. Pharmacokinetic Parameters of Hu BChE and Mo BChE in Mice

injection is in agreement with the lack of a humoral response to the injected enzyme. The observed extended stability of exogenously administered Mo BChE into mice and macaque BChE into macaques suggests that even a single injection of homologous ChE is sufficient to maintain the enzyme at a long-lasting therapeutic level. The results of both studies with two injections of BChE have clearly demonstrated the utility of homologous BChE as an effective and safe scavenger, exhibiting high stability and low immunogenicity in recipient animals. With respect to the potential use of Hu BChE in humans, these results are consistent with a reported in vivo half-life of 8-11 days and the absence of reported untoward immunological and physiological side effects following blood transfusions and iv injections of partially purified Hu BChE into humans.<sup>13-16</sup>

## Conclusions

Taken together, the pharmacological, safety, toxicity, stability, and efficacy data strongly support Hu BChE as a safe pretreatment for chemical agent intoxication. Pharmacokinetic parameters of Hu BChE in mice and guinea pigs suggest that a single dose of enzyme can maintain blood BChE at a therapeutic concentration for at least 4 days. Safety and toxicity studies demonstrate that Hu BChE, even at a dose that is

30 times the therapeutic dose, is devoid of tissue toxicity and is safe for human use. The Hu BChE has a long shelf life (2 years) in lyophilized form at temperatures ranging from 4-45°C. Similarly, the pharmacokinetic properties of the enzyme were not affected upon storage at -20°C to date (2 years). Pretreatment with Hu BChE protected guinea pigs against a 5 x LD<sub>50</sub> dose of GD or VX. As expected, injection of Hu BChE in mice elicited the production of high levels of anti-BChE antibodies. No antibody response was detected following either of the two homologous Mo BChE injections. The observation that the second injection of Mo BChE resulted in a pharmacokinetic profile that was similar to that of the first injection is in agreement with the lack of a humoral response to the injected enzyme. These results suggest that Hu BChE is a safe and effective bioscavenger that should be developed as a product that can protect humans against all OP nerve agents.

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# Five Keys to Deploying Activity-Based Costing

Ken Whittaker†

*The U.S. Army Medical Research and Materiel Command (USAMRMC) adopted Activity-Based Costing (ABC) in 2001 to determine the actual costs associated with the products and services the command produces. While instituting this new way of looking at the command's business processes, the command has recorded the lessons it learned to help other organizations about to embark on the same adventure.*

## Introduction

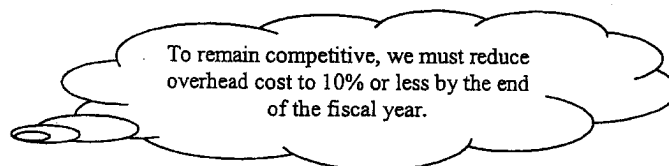
Even with the Department of Defense informative ABC Guidebook, finding definitive answers to questions about this new and evolving discipline can be difficult at times.<sup>1</sup> In fact, there are considerable differences of opinion among the experts on exactly what ABC is. For example, the United States General Accounting Office defines ABC as "a set of accounting methods used to identify and describe costs and required resources for activities within processes."<sup>2</sup> Other practitioners, such as Computer Aided Manufacturing International, clearly omit any references to accounting and define it as, "a methodology that measures the cost and performance of activities, resources, and cost objects. Resources are assigned to activities, then activities are assigned to cost objects based on their use. The ABC recognizes the casual relationship of cost drivers to activities."<sup>3</sup> The truth of the matter is, while ABC does apply sound accounting principles, you must use substantial professional judgement and creativity to implement it successfully. The following are five of the most important lessons the USAMRMC learned while implementing ABC.

We began implementing ABC in FY01 as a way to determine the actual cost associated with the products and services we produce. By FY02, 15 rapid prototype models had been completed for the laboratories, support units, and headquarters. To evaluate our progress, an internal survey was performed and the Army audit agency was asked to review and validate the models. While we are still in the early stages of implementing and using ABC, the lessons we learned may help other organizations reduce their learning curve, accelerate implementation, and achieve concrete results.

## Support by Top Leadership

First and foremost, you must have the support of top leadership. Perhaps this is so obvious that it should go without saying. Clearly, ABC will not succeed as a grass roots movement. And just like other changes, we began with the standard pronouncements of support for ABC by the Commander, followed by policy memos. While this is a starting

point, more than a simple mandate is needed to be successful.



Top leadership must develop a strong business justification for implementing ABC, set clear and measurable goals, and hold direct reports accountable for achieving them. In our case, MG Lester Martinez-Lopez, the Commanding General of the USAMRMC, explained at his Commander's Conference that to remain competitive in the future, we had to reduce overhead cost to 10% or less by the end of the fiscal year. As a result, there was no question about why ABC was being implemented, the results expected, the consequence of failure, and the necessary time frame.

It might be of interest to note that the implementation of ABC was not the primary goal. Remaining competitive by reducing overhead costs was the goal. The ABC was simply the vehicle to achieve the goal. While it may have been possible for the organizational elements to accomplish this goal without implementing ABC, it was unlikely. The current appropriations and budget-based accounting systems encouraged categorizing many costs as overheads and then simply allocating them arbitrarily to the products and services produced. The advantage of Activity-Based Costs is that it assigns costs based on the amount of resources used in order to provide the product or service, thereby greatly reducing the overhead cost category in the process. Consequently, the most practical method for achieving the goal was to implement ABC, and we encountered little resistance with the implementation.

## Focus on the Customer

Of the three major components of ABC (Resources, Activities, and Cost Objects), determining the cost objects was the most difficult task. A cost object is simply an activity, output, or item whose cost is to be measured. In today's environment of declining budgets, redirection of resources to the

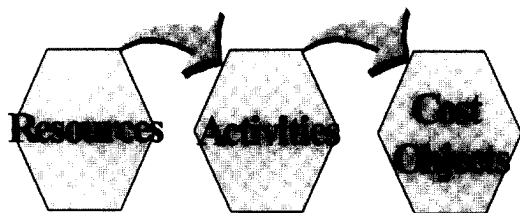
Army's combat mission, competitive outsourcing and top-down driven efficiency initiatives, we felt that we must focus on our outputs as cost objects to make sound data-driven management decisions to remain competitive.

Perhaps one of the most difficult tasks for research organizations is to identify their outputs, since research may not be applied to a final product for many years to come, if at all. In his book, *The Seven Habits of Highly Effective People*, Stephen Covey's second of the seven habits is: "Begin with the end in mind." Similarly, the easiest and most effective way to identify outputs is to first focus on the customer. By focusing on the external customers who consume the research products or services, the outputs become less obscure. An additional benefit of a clear customer focus is that it may help to identify products and services unwanted by the customer.

Without a genuine customer focus, the identification of the outputs can be flawed, causing disastrous results. For example, in our rapid prototype models, many of the laboratories identified a cost object, which they called "organizational sustaining." On further investigation, the "organizational sustaining" cost object turned out to be activities such as acquisition, logistics, resource management, etc, that were consumed internally. In other words, organizational sustaining was simply a new name given to what was previously called overhead. To make matters worse, with a separate organizational sustaining cost object, these costs were no longer reflected in the cost of the products or services that caused the cost.

### Value Exceeds Cost

In the research community, we are comfortable with data, lots and lots of data. In fact, in many cases, we view more data as better. However, this is not true with ABC. Complex models are difficult to maintain, and the data is expensive to gather. A complex model with excessive cost data is like micro-managing people unnecessarily. While we may be motivated by the details that a model can provide, the effect can be overwhelming, if not disastrous.



The ABC assigns costs in two stages. The first stage assigns the costs of resources to activities, and the second stage assigns activity costs to outputs. The pitfall comes in the first

stage of the process: assigning the costs of resources to activities. To avoid the potential "data dump," we choose to roll up all activities that did not account for at least one tenth of a full time equivalent (FTE). The 1/10 FTE rule worked well for us because as a labor intense organization, FTEs are one of our primary cost drivers.

Remember that ABC measures the cost of performing activities and assigns the cost to products and services. Focus on the accuracy of the big picture before deciding which activities to drill down into more detail.

### Learn from Thyself

In addition to accurate output cost, ABC provides the opportunity to seek out and study the best internal practices within the organization. By defining the business processes and activities and tracing their costs, ABC can identify the most cost effective practices within the entire organization. However, this can only be accomplished if the models are structured to compare like activities from the beginning.

For example, the U.S. Army Medical Research Institute of Chemical Defense has the same fundamental Human Resources' requirements for hiring and developing employees as does the U.S. Army Medical Research Institute of Infectious Diseases. Likewise, the Walter Reed Army Institute of Research has the same basic resource management requirements for accounting and budgeting as the U.S. Army Institute of Surgical Research. These processes, although performed at different laboratories, are common and can be benchmarked to produce superior performance if each model uses the same activities to drive costs. We didn't limit the benchmarking to support activities either. We identified common research activities for benchmarking, also.

For that reason, it pays to identify the common business processes and activities before modeling begins. Once the activities are defined, the costs can be traced, and the most cost-effective practices can be easily recognized and exported to other organizations.

### Build a Knowledge Base

While it is important to note that ABC and standard costing methodologies are not mutually exclusive, the concepts are very different. Don't assume that the existing accounting staff will understand ABC or embrace it. As a consequence, you may have to build the technical expertise and establish a core of key staff to set the stage for implementation and the use of ABC. While it may be tempting to hand-off the development of the model to hired consultants, it is just as likely that internal staff will be required also, because they are the only ones that

understand your business processes and activities well enough to develop meaningful models. We found that a senior position serving as a change agent who understands and can oversee the projected detail was crucial to our success.

In conclusion, ABC is an evolving discipline that requires substantial professional judgement and creativity to implement successfully. Nevertheless, the effort can translate cost data into a reliable information source, upon which management can make sound decisions that cannot be found with traditional accounting methods. We hope that you will benefit from the lessons we've learned by starting off on the right path and avoiding a few of the pitfalls along the way.

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# USARIEM: Physiological Research for the Warfighter

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*The annals of military history are replete with graphic examples of the devastating effects of environmental factors on the outcome of battles, campaigns, and wars. From the catastrophic effects of the winter of 1775-1776 on the Continental Army, the Russian winter on Napoleon's Army in 1812, to the heat-related injuries or deaths in the Egyptian/Israeli war in 1967, heat, cold, and high terrestrial altitude have repeatedly played key roles in the success or failure of military operations. The U.S. Army Research Institute of Environmental Medicine (USARIEM) conducts basic and applied research to determine how exposure to extreme heat, severe cold, high terrestrial altitude, occupational tasks, physical training, deployment operations, and nutritional factors affect the health and performance of military personnel.*

## Introduction

A significant research effort involving more than 1 million Soldier participants at more than a dozen Army installations explored the relationships between measurable physical characteristics and health and performance outcomes, including physiological assessments, strength and endurance measurements, and disease epidemiology. It also evaluated the impact of rations and coffee on performance and injury in exhausting foot marches. Although this sounds like recent USARIEM studies, these studies were described by Benjamin Apthorp Gould in 1864, based on Union Army Soldiers. The point is that military operational medicine research, the kind of research conducted by the USARIEM has been of special importance to the U.S. warfighter since the early days of the Republic. These issues continue to be of great concern and will be as long as warfighters are challenged to the limits of their mental and physical capabilities in harsh environments. These limits of warfighter capability are ultimately determined by metabolic processes – it is the challenge of USARIEM to conduct the research to continue to define and expand these metabolic limits.<sup>1</sup>

The mission of USARIEM is to conduct biomedical research to protect the health and performance of Soldiers in training and operational environments. This largely involves “enhancement” of the Soldier capabilities by preventing the degradation of health and performance in the face of external stressors that may include the natural environment or manmade exposures, including our own materiel systems. This article outlines the core competencies and accomplishments of USARIEM and highlights the current and future goals of the research program for the warfighter.

## Capabilities and Approaches

The USARIEM is co-located with Natick Soldier Center

in Natick, MA. It is the modern day successor to elements of the Harvard Fatigue Laboratory, the Fort Knox Armored Medical Research Laboratory, the Quartermaster Climatic Research Laboratory (Lawrence, MA), the Arctic Laboratory, and the Fitzsimmons/Letterman Army Nutrition Labs.<sup>2,3</sup> The Institute has approximately 170 employees including 50 credentialed principal investigators; 65 of the staff are uniformed Soldiers, including 20 officers. The mix of specialties ranges from physiologists and psychologists to biomathematical modelers, dieticians, physical therapists, physicians, physician's assistants, and veterinarians. The unit is optimally sized to function as a single integrated laboratory although it is administratively organized into four science divisions and a research support division. The science divisions are centered on core capabilities that involve environmental stressors and/or stressor countermeasures product lines: thermal and mountain medicine; military performance (exercise and psychology); nutrition and metabolism; and biomathematical modeling and biophysics. Most research studies and Science and Technology Objectives ([STOs], formally recognized research programs intended to address an important Army problem) require teaming across divisions, which is readily accomplished in this moderately small and hierarchically flat organization. Research management principles are summarized in Table 1. Principal regulatory functions are accomplished by committee: to include human use, animal use, credentialing, and quality assurance. Collocation with other research functions related to individual Soldier equipment and rations at the Natick Army post, and proximity to many great academic and technology centers in the Boston area provides a vital multiplier ranging from access to technical libraries to the availability of a highly skilled talent pool. Specialized capabilities include heat and cold chambers, immersion pools, altitude chambers, animal research facilities, biomechanics laboratory, exercise physiology labs, an in vivo bone research lab, and multiple biochemistry wet labs. Off-site laboratories include: an exercise physiology lab situated in

Wornack AMC, Fort Bragg, NC (the USARIEM Medical Research Unit – Fort Bragg), a laboratory facility on top of Pike's Peak, CO, lab space in other laboratories such as a genomics laboratory at Brigham and Women's Hospital in Boston, and direct support from key contractors, notably the Pennington Biomedical Research Center in Baton Rouge, and JAYCOR (TITAN) Corp in San Diego. The location near Boston permits strong collaborations with universities and high technology businesses concentrated in the area. Closely related research efforts also exist in military labs in Canada (DRDC-Toronto) and France (CRSSA, Grenoble). A new operational medicine research laboratory is just being formed by the Bundeswehr in Berlin.

Independent peer review is an essential part of the research process
Every study must be traceable to a relevant Army problem or program; even basic research must address a key technology barrier
Basic research is integral to a strong military physiology program, providing the scientific depth and intuition to address unforeseen problems and to make true advances
Opportunistic research needs to be carefully considered as it can produce high payoffs or major program distractions
Study priorities should favor our core strengths and rely on extramural partners in areas where we are not the recognized experts
Every study must culminate in an archived report, with open literature publications being most desirable

Table 1. USARIEM Rules of Research

The USARIEM vision is to transition biomedical research findings that are timely and practical to forces deployed anywhere in the world. The primary reason for the Army to have this intramural science capability with both uniformed and civilian scientists is to have experts dedicated to eliciting, conducting, harvesting, and translating relevant science that expands options for Army policymakers and combat and materiel developers. A reliable metric of in-house scientific expertise is peer reviewed publication, reflecting active involvement in leading edge science, full engagement with the larger scientific community, and actual productive work. The importance of publication to intramurally funded research cannot be overstated; if results of a study are not critically appraised and documented, the study essentially was never done and taxpayer dollars were wasted. In the past 5 years, USARIEM scientists averaged 2.2 primary publications per year, a high rate of productivity within the research community. While scientific publication is necessary, it alone is not sufficient to cross the completion line with Army research. Nobody else in the Army is expected to be reading the specialty journals or developing the subject matter expertise that is resident in USARIEM scientists. This experience must also be translated into direct benefits to the Army mission through

recommendations for policy and doctrine, guidance for materiel developers, and predictive models for training and mission planners. General categories of USARIEM products are listed in Table 2 and recent accomplishments for the Soldier are listed in Table 3.

<u>Provide recommendations for training policy and guidance</u> to enhance Soldier capabilities and reduce health risks ( <i>the Army may put young men and women in harm's way, but recruits are expected to come home even better than when they left</i> )
<u>Develop preventive medicine guidance</u> to save Soldier lives and reduce lost duty time and medical costs, as well as ensure long-term health even after they leave the Army ( <i>the challenge is to implement and institutionalize scientific knowledge through practical solutions</i> )
<u>Provide design specifications</u> to improve individual Soldier equipment and rations ( <i>we don't make the Soldier stuff; we make the stuff safer, more effective, and Soldier compatible</i> )
<u>Devise monitoring strategies and predictive algorithms</u> to prevent and detect performance decrements (which may also signal impending casualty risks) for Soldiers in training and in operational environments ( <i>we have better "prognostics and diagnostics" intelligence on our sophisticated vehicles than we do on the status of our own Soldiers</i> )
<u>Protect Soldiers and the Army mission from "good ideas"</u> that may harm Soldier health and performance ( <i>but be open-minded enough not to exclude surprising breakthroughs</i> )
<u>Protect against technological surprise</u> by conducting basic research to investigate and monitor all revolutionary ideas and to explore every potential advantage for the Soldier ( <i>"Intellectual capital becomes an important aspect of the future" – Ron Sega, DDR&amp;E, 2004</i> )

Table 2. Categories of USARIEM Research Products

## Recognized Science Leadership in Environmental Medicine

The USARIEM is internationally recognized as an authority in environmental medicine, with notable expertise in heat and dehydration. This evolved from classical studies on sweat responses and other desert adaptations, reflecting the Institute's origins in the Harvard Fatigue Laboratory, the Armored Medical Research Laboratory at Fort Knox, and the Quartermaster Climatic Laboratory in Lawrence, MA.<sup>3</sup> There is no other federal agency with a strong core program in this area and USARIEM scientists routinely served as consultants for a wide variety of other agencies on issues such as workplace heat standards for NIOSH, orbiter re-entry thermal challenges for NASA, national recommendations on water intake requirements by the Institute of Medicine, position statements on electrolyte drinks and hydration for the American College of Sports Medicine, and normal ranges of hemoconcentration for the U.S. Anti-Doping Agency. The research of USARIEM scientists is among the most highly cited in the world community of physiologists. For example, last year, six of the 20 most highly cited environmental physiology papers were produced by USARIEM scientists.

*Solutions for the warfighter today based on subject matter expertise and testing*

Rifle recoil limits to allow testing of new high powered shoulder-fired systems

New TB MED to reduce physical training injuries

Altitude guidance for operations in Afghanistan

"Red zone" model for heat strain guidance in chemical threat risk assessment

Fitness tracking software tool for DOD demonstration project at Fort Bragg

*Tech base research advances for near term solutions (for example, STOs)*

Microclimate cooling strategies that reduce power requirements by >50%

Protein requirements for high activity and low calorie intake

Redeployment neuropsychological assessments and associations with in theater exposures

Warfighter Physiological Monitor – Initial Capability System

Tyrosine effectiveness in sustaining mental performance under intense stress

*Basic research to develop and harvest potentially revolutionary advances*

Friend-foe discrimination in fatiguing and distracting vigilance tasks

Genomic profiles of heat stroke injury

Mineral micronutrition (zinc) requirements to sustain immune function

Biomechanical influences on mechanisms of bone remodeling

Insulin-like growth factor-I isoform responses to military operational stressors

*Table 3. What Has USARIEM Done for the Soldiers Lately ?  
Examples of Recent Accomplishments and Work in Progress  
(2003-2004)*

In WWII, Army physiologists developed simple methods for rapid heat acclimatization and this research was actually put to use on ships moving troops from the continental United States to North Africa in Operation Torch.<sup>4</sup> In the recent military actions in Southwest Asia, heat injuries were further minimized through hydration guidance as well as work-rest models that prevented unnecessary risk. Information was effectively distributed in 1991 through a pocket guide produced in a 1-week period by USARIEM scientists, as well as through new catch phrases to convey the knowledge (for example, "water as a tactical weapon"); in the past year, the most up-to-date science on acclimatization has been put into field guidance (Figure 1). Nevertheless, in 2004, Soldiers are still dying from heat stroke in both training and in deployments; these incidents were predictable and preventable with the available knowledge, indicating that we still have not been fully effective in translation of our knowledge into the protection of Soldiers.<sup>5</sup>

A new and relatively rare concern that surfaced in the past decade was a problem of excessive hydration and

hyponatremia, with training deaths caused by excessive water consumption. This led to new hydration tables with upper limits that were validated in hot weather training to ensure that the balance did not tip too far and lead to an increase in heat injuries.<sup>6</sup> Most recently, a program to enhance cooling efficiency with vasodilators, regional and intermittent cooling, and skin temperature feedback has produced a significant breakthrough that takes power-hungry microclimate cooling devices (for example, water-cooled garments) from interesting future concepts to power-efficient and effective near term reality.<sup>7</sup>



*Fig 1. Heat Acclimation Guide 2003. This is an example of the information products produced for preventive medicine activities based on USARIEM research and subject matter expertise.*

Cold research is also conducted at USARIEM. It is an unfortunate reality that preventive medicine is most appreciated following failures, not after successes that ensure the absence of adverse events. It is especially unfortunate if the first disaster does not lead to a substantive solution. For example, the Army suffered a large number of cold weather injuries in the Aleutian Islands during WWII through cold wet exposures that occurred when landing craft fell short of the shorelines. These high casualty rates against enemy forces that had already withdrawn reflected a gross underestimation of environmental risks. In 1976, hypothermia deaths in the swamp phase of the Ranger training school led to a comprehensive revision of the course and new immersion cold exposure tables from USARIEM based on best available data. In 1995, more hypothermia deaths in Ranger training led to new studies at USARIEM that have revealed previously unknown effects of repeated cold exposures and important interactions with other stressors that explain the occurrence of hypothermia at relatively mild water

temperatures.<sup>8</sup> Exposure guidance has again been revised based on these new findings and with new models developed in conjunction with expert colleagues at USARIEM's Canadian counterpart, DRDC-Toronto.<sup>9</sup> This knowledge has been captured in a new TB MED on cold injury prevention.

There is a much lower tolerance for risks in training than there is in operational emergencies where a commander may not have a choice in the assumption of risks; however, in either case, commanders need accurate assessments for their mission planning. In recent operations in Afghanistan, commanders knew that there were health and performance risks associated with rapid ascent to well over 10,000 ft in the Spin Ghar mountain range and they needed quick advice on how to best mitigate the risks. The USARIEM was the only institution in any federal agency that could provide this immediate expertise on what to expect and how to best prevent and treat problems with high altitude illnesses.<sup>10</sup> Soldiers were acutely impaired, where a 50 pound load felt like 100 pounds for unacclimatized troops reaching 10,000 ft, and at least one serious accident occurred in a helicopter evacuation of a suspected high altitude pulmonary edema emergency which may have been misdiagnosed. The special operations forces and the Army have both sponsored new efforts at USARIEM to develop rapid acclimatization strategies with intermittent hypoxia, explore nutritional supplements to boost performance at altitude (notably carbohydrate), and construct staging tables to provide recommendations on rates of ascent (similar to the concept of Navy dive tables). The USARIEM John Maher laboratory facility on top of Pike's Peak at 14,100 ft is currently the site of an important experiment to assess the relative advantage of having troops preacclimatized for rapid deployment to altitude, for example, mountain troops stationed at Fort Carson, CO (Figure 2).

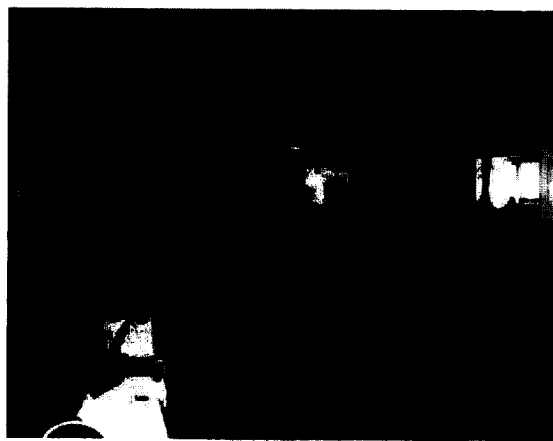


Fig 2. USARIEM Maher Laboratory on Pike's Peak, CO, at 14,100 ft. A current STO effort is collecting data from partially acclimatized individuals to determine how important this advantage is to rapid ascent in a military deployment.

Future advances are expected to emerge from current basic research investments in environmental physiology to include genomics research assessing the human building blocks of environmental injury susceptibilities, a joint effort by USARIEM scientists and the genomics laboratory at the Brigham and Women's Hospital in Boston.<sup>11,12</sup>

The natural environment is not the only source of important interacting stressors that can threaten the health and performance of a Soldier in training and operational environments. The key stressors that USARIEM studies (some in collaboration with WRAIR) are listed in Table 4, with highlighted blocks for current areas of concentration.

### Prognostics and Diagnostics to Prevent Soldier "System" Failure

Army vehicles are instrumented and monitored to an unprecedented degree as part of the "prognostics and diagnostics" strategies that allow them to keep running trouble-free for thousands of hours with only periodic maintenance. We have no comparable system for Soldiers even though existing technology makes the sensor engineering portion of this feasible today. The concept of physiological status monitoring of Soldiers provides one of the truly revolutionary breakthroughs in individual Soldier enhancement. Biotelemetry has been available for many years, ranging from sports watches for heart rate monitoring to patient instrumentation used in an intensive care ward. The novel technology is usually not the sensor, it is the algorithms that turn sensor data into useful predictive information. No one can glean much useful information from hundreds of raw heart rates streaming into a computer, but it would be immensely useful for a team leader or medic to access a signal that warns of an individual or a team headed for trouble based on a transparent algorithm that draws on combined sensor responses with high predictive reliability.<sup>13</sup>

The USARIEM is the center of this activity on Warfighter Physiological Status Monitoring. The near term initial capability version ("WPSM-IC") is part of an effort that requires building a self-sufficient prototype system to include sensors, integrating hub, and any needed communications, since no Soldier system is currently available to provide this engineering backbone for field validation tests. This WPSM-IC will have early version capabilities for live-dead detection, fatigue prediction from recent sleep and activity, heat strain predictions from heart rate and skin temperature, and hydration predictions from instrumented water intake measures (Figure 3). This "sensor suite" capitalizes on the most developed physiological models in sleep and fatigue from WRAIR and in heat and hydration from USARIEM.

	Countermeasure Product		
Stressor/Exposure	Training and Acclimatization	Nutrition and Metabolic Regulation	Models on Human Limits and Effects
Heat	Acclimatization markers (STP 3.T)	Water metabolism (STO 3.T)	Predictive algorithms (STO 3.H)
Cold		Tyrosine supplement (STP 3.I)	Exposure tables (STP 3.I)
Hypobaric Hypoxia	Rapid acclimatization (STO 3.J)	Carbohydrate supplement (STO 3.J)	Staging tables (STO 3.J)
Physical work	"Smart" training (STO 3.S)	Weight management (STP 3.0)	Neck fatigue model (STO 3.Z)
Energy deficit		Protein requirements (STO 3.B)	Energy bal measures (STP 3.H")
Biodynamic forces	Bone remodeling mechanism (STP 3.S)	Bone mineral accretion (STP 3.S)	Body armor eval STO 3.K (JAYCOR)
Neurotoxic chemicals*		Antioxidant supplement (Future)	Neuroepidemiology STP 3.M
Sleep deficit		Carbohydrates and caffeine (STP 3.B')	Fatigue-performance STO 3.Q (WRAIR)
Anxiety and fear	Stress resilience STO 3.W (WRAIR)	Stress markers (STP 3.B")	

\*Oxidative and inflammatory stressors

Note: Shading indicates areas of current USARIEM focus, with darkest indicating greatest investment; STOs are Science and Technology Objectives – programmed research approved by Army; STPs are Science and Technology Evaluation Packages – programmed research approved by the USAMRMC.

The focus of the research is on solving Soldier problems that almost always involve more than one stressor in field environments and where the interactions of stressors may be critical, such as sleep at altitude, changes in toxicity of materiel in the heat, work in a hypocaloric environment, etc.

Table 4. Environmental and Occupational Stressors Studied at USARIEM and Associated Laboratories

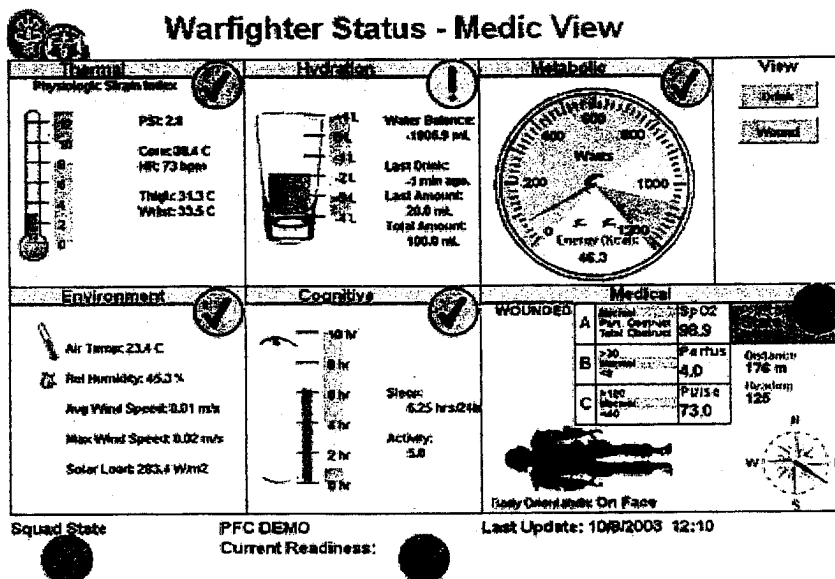


Fig 3. Notional Soldier readout presenting real time information on physiological status based on models and algorithms that interpret Soldier sensor data. In this example, hydration is low based on recent water consumption history and the prone Soldier may be casualty.

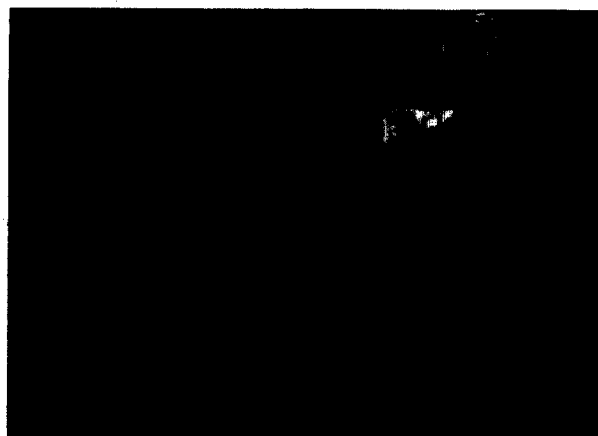


Future versions (for example, "WPSM-Commander") will provide enhancements that include estimates of energy flux ("fuel tank and RPM" equivalents), other environmental risk predictions ("engine temperature and oil level" equivalents), and improved real time analyses that include comparisons to ambient conditions, comprehensive Soldier databases and models, and individual Soldier history. Vital relevant information to a commander on a Soldier's mental status will be predicted from a minimal sensor set that might involve noninvasive measures such as nerve conduction velocity, eye movements, voice stress analysis, and Soldier task-embedded metrics, as well as improved neuropsychological predictions derived from environmental conditions and other status information. The greatest value for these sensor systems may be in training, where commanders and units learn their true limits before impending failure; however, plug-and-play systems tailored to a variety of specific mission requirements will undoubtedly find their way into every conceivable application. The goal of this monitoring is to help Soldiers effectively achieve the full range of their physiological capabilities, just as an athlete training to target heart rates or blood lactate levels uses physiology to achieve peak performance. From a USARIEM perspective, this is an opportunity to gather years of physiological data and algorithms into a useful integrated application for the Army.

Another example of a potential future system diagnostic/prognostic component is energy balance. Energy balance is an important physiological measure that may predict falling glucose levels that affect mental performance, limit physical endurance, predict impaired shivering thermogenesis, or predict the rate of heat storage. The USARIEM scientists have devised various methods to noninvasively assess voluntary energy expenditure based on biomechanical principals that can be incorporated into a "smart" boot that measures foot contact time.<sup>14</sup> This can even be combined with heart rate measures to provide an assessment of aerobic fitness level that might eliminate the need for periodic fitness testing for the future Soldier and help individuals in effective weight control.<sup>15</sup>

Another USARIEM diagnostic/prognostic tool is a heat strain monitor, a generational advancement of the old Wet Bulb Globe Monitor. Again, the main challenge is not in new discoveries for the hardware development, but in the advancement of research models that transform available data into useful knowledge. The algorithm used in a handheld USARIEM Heat Strain Monitor (with a version currently in use by the Australian mining industry) is an example of the applications that can be rapidly derived from a family of detailed and complex heat physiology models that have been developed through years of Army research.<sup>16-18</sup> Current efforts at USARIEM will merge location, Air Force weather data, and individual Soldier data to produce local environmental strain

predictions (for example, fluid intake requirements, work/rest cycle recommendations). Even the interactive effects of chemical prophylaxes and treatments will be predictable for hot environments, based on human studies previously conducted at the lab. This is important for current efforts to include heat strain predictions with environmental chemical sensors, to help balance a decision between the risk of some level of chemical threat agent exposure and the expected physiological tolerance an individual adopting mission-oriented protection posture under the existing environmental conditions (Figure 4). In addition to advancing research models to improve the predictions and drive towards prediction of individual variability, USARIEM modelers have been able to react quickly to current needs to provide heat/cold threat assessment tools to warfighters and commanders. For example, an environmental risk "Slide Rule" was developed for Ranger school cadre to read off the reasonable pace time for standard distance runs and road marches according to prevailing heat conditions, reducing serious environmental extremes risk to the Soldiers in training. This past summer, close monitoring of Ranger training events with elevated heat injury risk was explored through the use of a simple ingestible pill-based core temperature measurements in a few sentinel students.

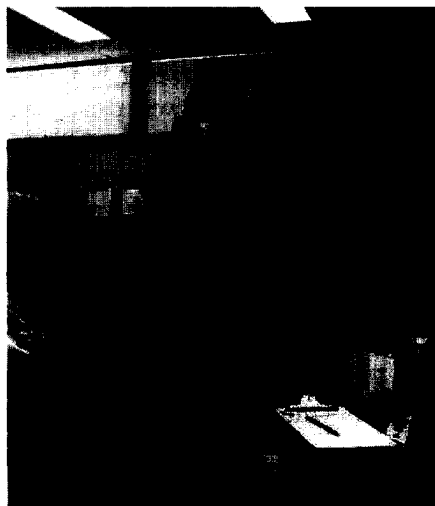


*Fig 4. Evaluation of the heat strain produced in chemical overgarments with Soldier participants exercising on a treadmill in the Doriot climatic chambers. Thermal physiologists at USARIEM have evaluated all chemical pretreatments and personal protective equipment before approval and fielding by the Army.*

### **Materiel Optimized to Human Tolerances – Biomedical Databases and Models for Virtual Prototyping**

The USARIEM has been instrumental in ensuring that the clothing and equipment developed for warfighters by the Natick Soldier Center is assessed against valid scientific research to determine the physiological cost to the user. For example, metabolic costs associated with backpack and protective equipment designs have been used to guide more efficient

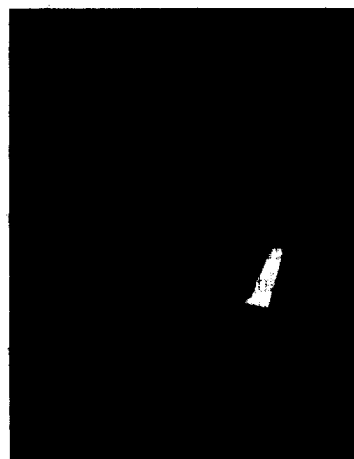
personal equipment designs. The increased energy requirements in cold weather are more related to the hobbling effect of bulky cold weather clothing than to heat production.<sup>19</sup> The design of load carriage equipment, protective gear, and even the tasks themselves can be optimized from these data and evolving models of load carriage (Figure 5).<sup>20,21</sup>



*Fig 5. Studies of energy cost produced by movement with various load configurations has led to design guidelines for scientifically optimized Soldier equipment. Many of these studies are conducted in the biomechanics research laboratory shared between USARIEM and the Natick Soldier Center.*

In addition, there are many examples of attempts to retrofit equipment, select Soldiers, or even re-engineer Soldiers (through training) to fit and operate equipment that was designed without adequate consideration to the human operator. Some remarkable examples came out of studies in the Defense Women's Health Research Program, with backpacks and safety equipment that were not compatible with female body proportions. Even before this, an entire USARIEM effort in the 1980s was focused on classifying Army jobs by physical demands, and for a brief period in Army history, recruits were steered away from high physical demand job specialties on the basis of a lift strength test. It has been since recognized that attempting to fit individuals to ill conceived equipment and task designs increases injury risk and impairs efficiency for both men and women. A recently completed USARIEM study considered this relationship between occupational strength demands and musculoskeletal injury rates. One military occupational specialty was selected as a representative specialty with very high injury rates (63B, light wheeled vehicle mechanic) to determine if injuries are indeed associated with mismatches between key task requirements and deficient strength capabilities of Soldiers performing the tasks (Figure 6). A separate and specific benefit of this study may be recommenda-

tions for improved design of the Future Combat System over the tasks required for maintenance of the HUMMV that did not fully consider the human element, specifically the physical requirements imposed on the mechanic.



*Fig 6. Field study conducted through the USARIEM Medical Research Unit, Fort Bragg. Light-wheeled vehicle mechanics are being studied to determine if injury rates are correlated with mismatches between the strength of the Soldiers and the strength requirements for key occupational tasks. This will determine if occupational strength training and testing may be of importance in heavy strength demand job specialties.*

### **Improve Physical Capacity Without Injury – Soldiers as Specialized Athletes**

Flat feet and underweight eliminated potential Army recruits in the last century. We now know from USARIEM research that individuals with high arches have the highest risk of injury and flat feet could be protective although there is inconsistency even in the evaluation of arch status between assessors.<sup>22</sup> Modern body composition standards have focused on overweight as a marker of fitness habits rather than underweight as an indicator of poor health and inadequate strength. Fat standards have been in place for the past 20 years, although it is entirely possible that we will return to inclusion of underweight standards in the future to ensure minimum lean mass to ensure adequate strength and reduce injuries for common tasks. Biomedically-based standards for entry and retention to the Army have been actively investigated by USARIEM with extensive collaborations in the past with the Naval Health Research Center, San Diego.<sup>23</sup>

There is a common perception that we don't need more research in sports physiology because all the important science is known or is being done elsewhere and, furthermore, all necessary information can gleaned from popular fitness

magazines. This partly reflects the fact that everyone is an exercise "expert" based on their own anecdotal experience and usually without an appreciation for the potential applications of emerging science such as the discovery of myostatin's role in regulating muscle satellite cells and the effects of local IGF-1 production on muscle and bone that may accelerate tissue repair and remodeling in the future. Although the entire exercise physiology program at USARIEM is relatively small, this represents a national lead in physical performance research, especially in training studies, with no other federal agency sponsoring significant efforts in optimizing physical performance of healthy individuals, and no other military service currently conducting an organized research program in this area. The influence of USARIEM researchers in the exercise physiology community is highlighted by large representation of our scientists in the professional activities of the American College of Sports Medicine (ACSM), including as senior editor of the primary journal of the ACSM and in the authoring of many of the organizations position statements.

Current USARIEM efforts in physical performance are focused on physical training studies to determine modes of exercise that will provide specific benefits and to simultaneously explore the underlying mechanisms of bone and muscle remodeling that signal both healthy adaptations and maladaptive responses that may lead to muscle injury and stress fracture. Within the past few months, a new TB MED on physical training and injury prevention has been developed, and new guidance to reduce running injuries in basic training has been established for Army-wide implementation in collaboration with CHPPM.<sup>24</sup>

Bone biology is an example of USARIEM's multidisciplinary and integrated approach to addressing important Army problems, where the way we train, feed, and treat young men and women may, in combination, affect risk of stress fracture and longer term risks of osteoarthritis and osteoporosis. The fundamental principles that are derived from well-designed basic research studies can be particularly useful to scientists trained to recognize breakthrough findings that are relevant to military applications. For example, a discovery about biomechanical stress responses at the cellular level suggests that breaking up physical training into multiple daily sessions might provide more beneficial stimulation to bone than that produced in a single more intensive daily session, and this can now be further tested in a hypothesis-driven study. Monitoring impending risk of injury is also an active area of basic research investigation.<sup>25,26</sup> An overuse injury model that is being developed by JAYCOR in collaboration with USARIEM will further test predictions and helps focus research hypotheses based on existing and emerging bone injury data. In addition to bone remodeling studies, muscle injury and repair mechanisms are being pursued, including related topics that are important to

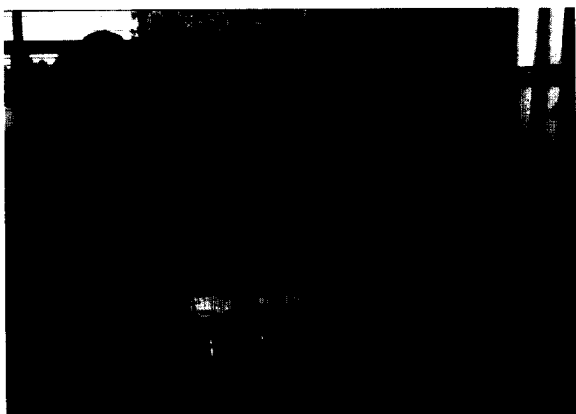
protecting young Soldiers in training such as rhabdomyolysis and exertional heat injury. In addition to the internal efforts of USARIEM scientists, extramural studies are leveraged to assess and improve physical performance on behalf of the Army. One recent Army-sponsored study at Ohio University debunks the concept of a "female athlete triad" syndrome, where women who exercise intensively do not, in fact, shut down their reproductive cycles as long as they reasonably match energy intakes to energy requirements; however, women who surpass a threshold of energy deficit with severe dieting are at increased risk for bone loss.<sup>27</sup> Such highly relevant extramural studies complement and augment the limited capacity of one small Army research lab and, as in this case, can produce immense payoffs in early translation by USARIEM experts to Army policies such as those involving fitness, weight control, and high intensity training.

### **Metabolic Enhancement and Nutritional Stress Countermeasures – the good, the bad, and the ugly**

In WWI, the Army was concerned about defining energy and nutrient requirements for various Soldier cohorts such as units primarily composed of specific ethnic European groups to ensure adequate provisioning of each group. The concept was discouraged by a panel of scientific advisors that formed the nucleus of nutrition research in the U.S., and also founded the Food and Nutrition Board that later became part of the Institute of Medicine. In the past decade, this concept of metabolic tailoring for individuals resurfaced and USARIEM addressed it through a series of studies in collaboration with the Pennington Biomedical Research Center in Baton Rouge, reviewed by the Committee on Military Nutrition Research under the same Food and Nutrition Board. Even Special Forces Soldiers behaved in a highly predictable manner as they exercised to exhaustion, stepping from glycogen metabolism to fat metabolism with greater homogeneity than the most skeptical energy balance scientists had predicted. Other studies explored metabolism and energy requirements in extreme environments ranging from extreme cold in tents in Alaska to high altitude runway construction by SeaBees in Bolivia. The true benefit of this series of studies was to demonstrate that carbohydrate supplementation during work could substantially extend performance. This successfully completed Army STO provided the technical data package to support the fielding of the Hooah bar and ERGO drink, two different forms of carbohydrate supplementation for Soldiers.<sup>28</sup>

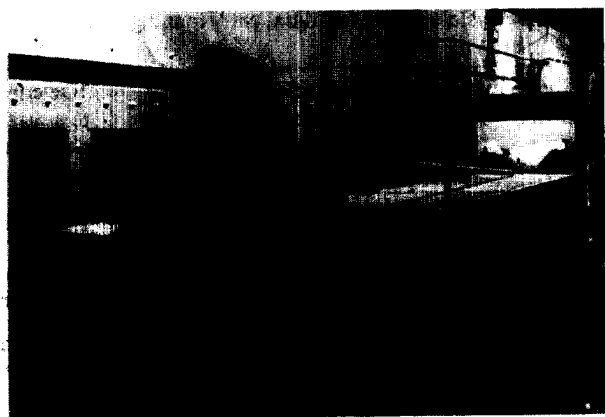
At least equally important to creating new options for health and performance of Soldiers is the role of USARIEM experts in protecting the Soldier against perhaps well-intended but bad ideas. Individually tailored rations would have been costly and diverted Army energy to an improvident effort but probably would have created little harm. Similarly,

entrepreneurial fads such as "structured" water and oxygenated water, egg whey proteins, etc. may be expensive and distracting but generally harmless. Other solutions that have been proposed, such as a pure fat diet to provide a compact energy-dense assault ration could be quite harmful, causing serious gastrointestinal distress and, for some Soldiers, chronic problems and performance degradation. The concept that U.S. Soldiers will eat almost anything if they are hungry enough is another common fallacy that is periodically resurfaced to USARIEM nutrition researchers, even though this was addressed long ago in a wide range of nutrition studies on pure gelatin, pemmican, and other specialized diets.<sup>2</sup> During WWII, an Army physician tracked maneuvering troops through the North African desert by following discarded K rations that, although "nutritionally complete" on the basis of the latest science, were "left untouched even by the desert rodents."<sup>29</sup> Some of the bad ideas in Soldier nutrition emerge where experimental data is lacking, providing a marketing penetration opportunity to any entrepreneur with a reasonable sounding claim. An important research gap currently being addressed under a new Army STO is the protein requirement when inadequate calories are available, such as on a relatively short mission where weight restrictions may prohibit carrying a full load of rations. This problem of providing an optimized and digestible minimum weight and volume supplement rather than leaving the Soldier to field strip rations down to a few random items that they choose to carry was identified as a key research requirement in a 1944 War Department memorandum. Although aspects of this question were addressed in the 1970s at the Jungle Warfare School, only now, with new technologies such as stable isotope labeled substrates and improved understanding of metabolism, can we finally address the protein requirements (Figure 7).<sup>30</sup>



*Fig 7. Food preparation kitchen in the Doriot climatic chambers. Research dieticians prepare specialized meals consisting of precisely characterized homogenates with varying protein content for a study to determine protein requirements of healthy young Soldiers working in a hypocaloric environment.*

Most people would agree that Soldiers should be provided every advantage that biomedical research can safely provide, including supplements and training methods that might be considered unfair in sports competition. However, many of the ergogenic aids that change performance by hundredths of a second and make the difference between a gold medal and no medal have little relevance to success on the battlefield. Thus, substrates such as creatine clearly work but may not provide the kind of advantage that benefits Soldier performance.<sup>31,32</sup> Stimulants such as caffeine clearly work, including at levels that would be banned in elite sports competition as unfair, and is being considered for fielding in gum and food bars (Figure 8).<sup>33</sup> Metabolic triggers such as carnitine do not wreak metabolic havoc with every meal and thankfully do not appear to work in healthy humans, where they might actually damage mitochondria if transport systems and biochemical pathways would actually allow it. Neurochemical precursors such as choline do not provide any measureable benefit and may leave an individual smelling like rotting fish, but tyrosine appears to provide important benefits in mitigating severe stress effects on mood and cognition and is being further investigated in human cold exposure studies.<sup>34</sup> The USARIEM studies have demonstrated the very potent ergogenic benefits produced by methods to boost the oxygen carrying capacity of the blood (for example, intermittent hypoxia training; erythropoietin; autologous blood transfusions) and these might be useful in special cases for elite troops and in high altitude operations.<sup>35,36</sup> The promise of storing water like a camel using glycerol hyperhydration failed to materialize into a clear performance or thermal protection benefit.<sup>37</sup> Antioxidants have been repeatedly investigated in the prevention of delayed onset muscle soreness, at altitude, and in other performance studies, with no clear



*Fig 8. Psychometric research laboratory instrumented for automated marksmanship and vigilance testing. A study participant is being tested for friend-foe discrimination in a sentry duty task that involves distracting stimuli and several hours of concentration. Caffeine sustains judgment over several hours of concentration while common medications such as some antihistamines impair Soldier discrimination and performance.*

benefit to the Soldier, some level of oxidative stress may even be important to stimulating normal processes of adaptation.<sup>38</sup> Investigation of antioxidant benefits in the mitigation of long-term health consequences in Soldiers is likely to continue at USARIEM.

## Conclusions

It's not enough to recruit healthy young men and women and later return them safely to their families; we now try to return them better than when they joined the Army with the promise that they will "be all they can be." With this comes the concept that the Army will accept any healthy recruit and provide them the scientifically sound metabolic and physiological tools for success. The USARIEM research is directed at ensuring that scientific soundness and further ensuring the protection and enhancement of the health and performance of all warfighters. The USARIEM research effort with thrust areas and core capabilities aligned with near and far term applications is captured in Table 5. Current efforts to

understand the fundamental metabolic processes underlying the responses to operational stressors, most importantly the neurophysiological responses that affect cognitive, psychomotor, and emotional status, are critical investments in the health and performance of the future Soldier.<sup>39,40</sup>

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Research Goals for the Soldier (core capability)	Current	Near-term (for example, STOs*)	Mid-term (current/ planned)	Far-term (basic research)
Own the Environment (Environmental physiology)	Demonstrated feasibility of physiologically-based microclimate cooling	*Develop predictive models and strategies for rapid acclimatization to altitude	*Improve hydration data and monitoring methods to counter dehydration and reduce logistics	Explore genetic markers of susceptibility to environmental injury
Optimize Materiel to Human Tolerances (Biomechanics)	Established biomechanically-based design criteria for load carriage equipment	*Assess neck injury thresholds for helmet design criteria	Study mobility: artificial limbs, extremity body armor, and prototype exoskeleton devices	<i>Integrate biomechanical injury and performance models for virtual design prototyping</i>
Extend Physical Capacity Without Injury (Exercise physiology)	Provided new science-based training guidelines for initial entry training	*Determine specific training strategies for rapid train-up without injury	Develop strategies to eliminate stress fractures in initial entry training	<i>Investigate strategies to enhance bone and muscle repair</i>
Metabolic Enhancement (Nutrition science)	Identified dietary supplements to improve physical task performance	*Determine protein req'ts to sustain mental performance with hypocaloric rations	Develop effective weight management strategies that enhance Soldier readiness	<i>Explore nutrient partitioning strategies to metabolize fat and preserve lean tissues</i>
Monitoring to Prevent "System" Failure (Biomathematical modeling)	Reviewed heat strain decision model for integration with area chemical detectors	*Develop initial capability Warfighter Physiological Status Monitoring system	Expand real time data handling capabilities and analysis of energetic for Soldier Status monitoring	Define approaches to noninvasive monitoring of cognitive status and readiness
Post Deployment Neurological Health (Neuro-epidemiology)	Compared effectiveness of neuropsychological health monitoring strategies in deployment	Determine methods to assess neurological health effects of materiel (permethrin, JP8)	Identify important interactions of deployment stressors for better neuroprotection	<i>Explore behavioral strategies to regulate neurochemistry to optimize resilience</i>
Ensure Effectiveness of Protective Equipment (Oxidative and Inflammatory Stress)	Validated threshold for shoulder injury from weapon recoil systems	*Develop new injury-based assessment system for body armor protection	Identify biochemical and physiological markers to assess tissue injury	Explore intrinsic antioxidant protection against mechanical and toxic hazards

\*Science and Technology Objective (STO): italics signify a USARIEM planned and/or current extramural effort

Table 5. Examples of Completed, In Progress, and Future Research Objectives for Metabolic Enhancement of the Soldier

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# Dietary Supplement Intake in the Active Duty Enlisted Population

MAJ Karen Brasfield, MS, USA†

## Introduction

In the last decade, regulation of the dietary supplement industry changed dramatically. For many years, the Food and Drug Administration (FDA) closely regulated dietary supplement ingredients under the provisions for food additives of the Federal Food, Drug, and Cosmetic Act to ensure that they were safe and wholesome. During this time, dietary supplements were subject to the same regulatory requirements as were food and drug products (prescription and over-the-counter).

In October of 1994, Congress enacted the Dietary Supplement Health and Education Act (DSHEA). This act essentially deregulated the dietary supplement industry. The DSHEA holds manufacturers responsible for determining that the dietary supplements they produce or distribute are safe. Manufacturers are also required to substantiate, by adequate evidence, any nutrient or health representations or claims made. Manufacturers are not required to register with the FDA or obtain FDA approval before producing or selling their dietary supplements. The FDA is responsible for taking action against any unsafe dietary supplement product only after it reaches the market.

The number of products available and the accessibility to consumers has grown at a rapid rate since the DSHEA. Current information on supplement use stems primarily from market information and studies that have focused on specific populations.<sup>1</sup> A 1996 survey estimated that consumers spent more than \$6.5 billion dollars on dietary supplements; this figure increased to greater than \$12 billion in 1998, and in 1999 an estimated \$15.4 billion.<sup>2,3</sup> The number of manufacturers producing supplements has increased as well. According to an FDA study, over 1,500 manufacturers produce dietary supplements. These data may suggest an increase in consumption in the American population, and not an increase of over 400% in sales prices of these products. However, because cost, frequency of use, and number of consumers affect sales, these data are not useful for estimating the prevalence of use in absolute or even relative terms.<sup>4</sup>

## Intake in the General U.S. Population

Studies were conducted on demographic and lifestyle

characteristics of users of supplements prior to the 1994 deregulation of the industry. However, since that time, a comprehensive study incorporating all dietary supplement categories has not been conducted.

Several studies have demonstrated an increase in consumption over the years. Data from the National Health Interview Survey in 1992 indicated that 24% of the U.S. population used vitamin and mineral supplements daily.<sup>5</sup> The third National Health and Nutrition Examination Survey (NHANES III) in 1988-1994, revealed 40% consumed vitamin and mineral dietary supplements in the previous year.<sup>6</sup> The Gallup Organization found in 1996, about 1 adult in 5 was taking herbal supplements.<sup>7</sup> A 1997 study of 40,000 households reported 68% of those surveyed, at least one person had used one or more of the 97 supplements noted in the survey at least once in the previous 6 months study.<sup>8</sup>

## Dietary Supplement Intake in Athletes

Athletes frequently use dietary supplements with the belief that such supplementation can provide them with a competitive edge and enhance their performance. Studies have shown that some athletes consume dietary supplements at a slightly higher rate than the American population, and in particular, they consume purported performance enhancers. A meta-analysis of 51 studies on the prevalence of dietary supplement consumption in athletes reported varying patterns exists by sport, with an average prevalence of 54% including all studies.<sup>9</sup> One hundred percent of the surveyed body builders, weight lifters, and female ultra-marathoners were consuming supplements. The studies included in this analysis were all conducted prior to the 1994 DSHEA and rapid increase in total sales.

A 1998 survey of 13,914 collegiate athletes revealed use of creatine (13%), amino acid supplements (8%), and dehydroepiandrosterone (1%).<sup>10</sup> A more recent study surveyed 16 universities to determine dietary supplement intake in Division IA college athletes (n=330).<sup>11</sup> Seventy-nine percent of men and 65% of women indicated consuming dietary supplements during their college athletic careers. The most prevalent type of supplement used in this population was creatine (28.6%), which men were more likely than women to consume. In addition, vitamin and mineral supplements were consumed (18.9%) by respondents, with more women (29.3%) than men (13.2%) using these. Again, a difference in use



was reported among different sports. Athletes involved in football and baseball were significantly more likely to use creatine than athletes in other sports.

### Dietary Supplement Intake in Select Army Populations

Most active duty military personnel are excluded from national health behavior surveys, and there are few published studies of the prevalence of supplement use in the active duty military population.

Kennedy and Arsenault found that 64% of male Soldiers (n=2215) entering U.S. Army Special Forces and Ranger training schools reported current use of dietary supplements.<sup>12</sup> Rangers and Special Forces reported choosing supplements they believed might enhance physical performance, increase energy levels, or improve general health. Multivitamins were being consumed by 37.4% of the subjects, and 20% were consuming vitamin C tablets. Twenty-nine percent were consuming a form of performance enhancing supplement, amino acid, or protein supplement.

A survey of the Navy Sea, Air, and Land personnel reported a consumption rate of 71%.<sup>13</sup> Primary reasons for consumption were to increase muscle mass, strength and power, provide an energy source, and improve general health. Remarkably, 32% reported consuming four to nine supplements concurrently, 34% consumed three, and 18% consumed two.

A survey on use of creatine and other supplements by members of civilian and military health clubs was conducted and of the 133 military personnel participants, 65% reported supplementing with vitamin(s), 47% mineral(s), 45% protein, 29% creatine, 21% herbal, 13% androstenedione, 10% beta-hydroxy-beta-methyl butyrate, and 3% anabolic-androgenic steroids.<sup>14</sup> These data suggest the respondents were consuming multiple dietary supplementations during the survey time period. This survey also included questions concerning where information was obtained concerning creatine supplementation. A Registered Dietitian (RD) was consulted by only 10% of respondents, while 14% consulted a physician. Sixty-nine percent reported obtaining information from a magazine. In addition, adverse events were self-reported by 45% of the current creatine users (including civilian personnel). The most commonly reported adverse effects included 20% gastrointestinal problems, 15% muscle cramping/spasms, and 13% reported dehydration.

Currently, as to this authors knowledge, there has not been a published study assessing dietary supplement consumption rates or reasons for consuming in the Army active duty enlisted population. Furthermore, little is known about consumption rates of purported weight loss supplements.

Casual comments by health care providers suggest that there is widespread dietary supplement use among the Army active duty population. Anecdotal evidence suggests that women are using dietary supplements for weight loss prior to the biannual weigh-ins and physical fitness test, and that males are consuming high-levels of performance enhancing dietary supplements. This study was conducted to assess the prevalence of dietary supplement consumption for Army dietitians and military health care providers.

### Adverse Events Associated with Dietary Supplements

Dietary supplements are not always benign, and risks have been associated with consumption. "Natural" does not necessarily equate to "safe," and studies have shown that supplements may cause significant harm or even death to those who consume them.

The FDA defines an adverse event as an incident of illness or injury that may be associated with a product or ingredient. The nature of these effects can range from minor complaints to potentially serious health problems, even death. Adverse events can result from direct toxicity, interactions with other medications, a contaminant in the supplement, or long-term/prolonged use.

In 1993, the FDA established an Adverse Reaction Monitoring System (ARMS) to collect and systematically investigate adverse and toxic effects reported with the use of dietary supplements. Reporting of these events is entirely voluntary. Adverse event reports can enter the FDA's passive surveillance ARMS through several means, such as the Drug Quality Reporting System, MedWatch (a computerized reporting system) programs, U.S. Pharmacopoeia, and FDA field offices. Other means available include the consumer complaint system, State Health Department, Poison Control Center health professionals, manufacturers, written and electronic correspondence, and written documentation of telephone conversations.<sup>15</sup> Adverse event reports typically do not generate conclusive evidence about the safety of a product or ingredient. Rather, the system is meant to signal possible public health risks. As trends are analyzed, the FDA can issue a warning to the public.

It is questionable, however, especially in situations where only minor complaints are experienced (for example, light headache or muscle cramp), whether most people will report these effects to local health authorities and the FDA's ARMS. Hence, because of under-reporting, published accounts of adverse effects from the intake of nutritional supplements may not reflect the entire scope of possible health and safety risks.<sup>16</sup>

A recent FDA-commissioned study estimated that less



than 1% of all adverse events associated with dietary supplements are reported to the FDA. Among the factors that may contribute to under-reporting are that many consumers presume supplements to be safe, consume these products without the supervision of a health care professional, and may be unaware that the FDA regulates them.<sup>17</sup> Another factor that may contribute to low reporting is that manufacturers are not required by law to collect data about adverse events or to report this information to the FDA.

### Sources of Information for Dietary Supplements

Individuals use a variety of sources to learn about dietary supplements ranging from peer-reviewed scientific literature to magazines written by lay people promoting fitness. College varsity athletes reported their group received information from magazines (21%), coaches (11%), family member (5.5%), friend (3%), and television (2.3%).<sup>11</sup> Additionally, they found that those individuals with greater nutrition knowledge were less likely to capriciously include supplements in their diet. Family practice patients reported sources of information on dietary supplements were media (27%), physician (22%), general knowledge (21%), family or friends (20%), and other health care professionals (5%).<sup>18</sup>

### Methodology

Subjects of this study were active duty enlisted Army male ( $n=750$ ) and female ( $n=124$ ) Soldiers from 16 Army posts located within the U.S. Army active duty RDs from different posts volunteered to participate in data collection. All company grade units at the 16 participating posts were included in a pool for random selection. Excluded from selection were all Active In Training (AIT) units, and basic training units, because personnel assigned to AIT and basic training units are prohibited from consuming dietary supplements during training in accordance with Army Regulation (AR) 612-201. Also excluded were units assigned to the post, but deployed outside the U.S.

The questionnaire consisted of 15 questions. The first eight questions focused on demographic data such as age, gender, self-reported height and weight, current pay grade, and estimated frequency of aerobic and anaerobic exercise during the previous 6 months. The next four questions examined consumption of dietary supplements during the previous 6 months, including current frequency of use (rarely or never, 1 to 2 times per week, 3 to 4 times a week, or 5 times a week or daily) and reasons for use (performance enhancer, promote general health, physician directed, researched or read about it, recommended by family or friend, recommended by sales person, or to prevent illness). For dietary supplements not listed on the questionnaire, the participants were instructed to write the

name of the supplement on the questionnaire and indicate estimated frequency of use and reasons for consumption.

The final three questionnaire items obtained information on the various establishments where participants routinely purchased supplements, where they obtained knowledge or information, and if adverse effects were experienced while consuming dietary supplements.

The investigator contacted company (unit) commanders of the randomly selected units to obtain their consent for the study. All company commanders consented to participate, except for one unit that was under orders to deploy to an overseas destination the following week. Questionnaires were distributed during May and June of 2002. Study participants were recruited according to research protocol guidelines established by AR 70-25.

Statistical analysis was performed using Statistical Package for the Social Sciences (version 11) software. Descriptive data were calculated as frequencies. Associations between supplement use and selected demographic variables, exercise habits, and sources of information were assessed by chi square test of independence. Chi square analysis was performed on nonparametric variables to determine if there were associations between supplement use and variables of interest. Independent  $t$  tests were performed to determine if there were significant differences in continuous variables between supplement users and nonusers. The criterion for significance was defined as  $P<0.05$  for all analyses.

### Results

A total of 1,300 surveys were mailed to 16 military installations for participation. The primary investigator distributed 100 questionnaires to two additional military installations. Two of the 16 installations that were sent questionnaires for distribution did not return data for inclusion. A total of 818 questionnaires were returned in the mail, and 73 distributed by the primary investigator were returned. Seventeen questionnaires were not included due to insufficient data on the questionnaire. A total of 874 questionnaires were used in the analysis for this study – a survey response rate of 64%.

The final sample consisted of 874 participants: 750 were male and 124 were female; participants' age ranged from 17 to 49 years of age; mean age was 24.90 ( $SD \pm 6.33$ ). Participants reporting consumption of dietary supplements, mean age was 25.32 years ( $SD \pm 6.44$ ). The mean age of males was 24.89 ( $SD \pm 6.40$ ); females' mean age was 24.96 years ( $SD \pm 6.00$ ). Demographic and other characteristics of participants are shown in Table 1.

Five hundred and thirty-one participants (60.9%) (444

	Supplement Users (n = 531) a	Nonusers (n = 343)
Age (years) b	25.33 (6.45) b	24.23(6.12)
Males	444	306
Females	87	37
Ethnic group		
White	305 (57.4) c	187 (54.5)
Black	99 (18.6)	78 (22.7)
Asian	20 (3.8)	14 (4.1)
Native American	10 (1.9)	5 (0.3)
Hispanic	70 (13.2)	44 (12.8)
Other	23 (4.3)	11 (3.2)
Military Rank		
E-1	53 (10.0)	57 (16.6)
E-2	64 (12.1)	46 (13.4)
E-3	87 (16.4)	46 (13.4)
E-4	139 (26.2)	99 (28.8)
E-5	80 (15.1)	40 (11.7)
E-6	69 (13.0)	33 (9.6)
E-7	35 (6.6)	16 (4.7)
E-8	4 (.8)	4 (1.2)
Body Mass Index (kg/m)	25.7 (3.32) b	24.93 (3.15) b
Aerobic Exercise		
Rarely or Never	14 (2.6)	18 (5.2)
1-2 times per week	79 (18.3)	32 (9.3)
3-4 times per week	273 (51.4)	189 (55.1)
5 times or more per week	165 (31.1)	104 (30.3)
Anaerobic Exercise		
Rarely or Never	14 (2.6)	14 (4.1)
1-2 times per week	109 (20.5)	87 (25.4)
3-4 times per week	255 (48.0)	153 (44.6)
5 times or more per week	153 (28.8)	89 (26.0)

a Use defined as one or more time per week. b Mean  $\pm$  SD. c Percentages in parentheses.

*Table 1. Demographic Characteristics and Health Habits of Supplement Users and Nonusers (N=874)*

males, 87 females) reported consuming at least one dietary supplement, one or more times per week. Significantly more females (70%) than males (50%) reported consuming a dietary supplement ( $P < 0.05$ ). Participants reported consuming a total of 1,841 dietary supplements for an average of 3.5 supplements

per user. The types and percentages of supplements consumed are shown in Table 2. Approximately 25% of the 531 supplement users reported consuming only 1 supplement, 22% consumed 2 supplements, and 53% reported consuming 3 or more different dietary supplements.

	Use 1-2 times per week	Use 3-4 times per week or daily	Use 5 times per week or daily
<b>Vitamins and Minerals</b>			
Multivitamin	85 (16.0)	65 (12.2)	150 (28.2)
Prenatal vitamin	2 (<1)	0 (0)	12 (2.3)
Beta-carotene	5 (<1)	4 (<1)	3 (<1)
B-Complex	21 (4.0)	8 (1.5)	6 (1.1)
Calcium	42 (7.9)	30 (5.6)	34 (6.4)
L-Carnitine	3 (<1)	6 (1.1)	3 (<1)
Folate/Folic Acid	14 (2.6)	6 (1.1)	2 (<1)
Iron	29 (5.5)	22 (4.1)	17 (3.2)
Pantothenic Acid	2 (<1)	2 (<1)	2 (<1)
Potassium	28 (5.3)	20 (3.8)	9 (1.7)
Vitamin A	29 (5.5)	23 (4.3)	16 (3.0)
Vitamin B6	21 (4.0)	20 (3.8)	8 (1.5)
Vitamin C	54 (10.2)	54 (10.2)	39 (7.3)
Vitamin E	35 (6.6)	27 (5.1)	19 (3.6)
Zinc	10 (1.9)	8 (1.5)	11 (2.1)
<b>Performance Enhancing</b>			
Androstenedione	7 (1.3)	10 (1.9)	9 (1.7)
Beta-hydroxy-beta methyrate	2 (<1)	5 (<1)	9 (1.7)
Carnitine	9 (1.7)	4 (<1)	9 (1.7)
Creatine phosphate	47 (8.9)	34 (6.4)	41 (7.7)
Chromium picolinate	9 (1.7)	8 (1.5)	17 (3.2)
Choline	2 (<1)	2 (<1)	0 (0)
Coenzyme Q10	2 (<1)	2 (<1)	1 (<1)
Dihydroepiandrosterone	5 (<1)	3 (<1)	2 (<1)
Dihydroxyacetone & pyruvate	4 (<1)	5 (<1)	3 (<1)
Ephedra, ephedrine, Ma huang	33 (6.2)	22 (4.1)	58 (10.9)
Glucosamine	10 (1.9)	5 (<1)	16 (3.0)
Tryptophan	2 (<1)	2 (<1)	2 (<1)
Amino Acids	13 (2.4)	14 (2.6)	26 (4.7)
<b>Herbal</b>			
Evening Primrose	2 (<1)	0 (0)	2 (<1)
Echinacea	22 (4.1)	3 (<1)	6 (1.1)
Feverfew	3 (<1)	0 (<1)	1 (<1)
Garcinia Cambogia Hydroxycitric	5 (<1)	1 (<1)	14 (2.6)
Guarana	8 (1.5)	8 (1.5)	20 (3.8)
Ginseng	54 (10.2)	32 (6.0)	24 (4.5)

Table 2. Number and (Percentages) of Total Soldiers Reporting Use of Dietary Supplements (n=531)

Ginko biloba	25 (4.7)	15 (2.8)	11 (2.1)
Garlic	39 (7.3)	18 (3.4)	15 (2.8)
Kava Kava	6 (1.1)	2 (<1)	1 (<1)
Saw Palmetto	0 (0)	2 (<1)	4 (<1)
St John's Wort	8 (1.5)	5 (<1)	6 (1.1)
Yohimbe, Yohimbine	9 (1.7)	2 (<1)	4 (<1)
Valerian	2 (<1)	2(<1)	0 (0)

Table 2. Number and (Percentages) of Total Soldiers Reporting Use of Dietary Supplements (n=531) (con't)

Vitamins and minerals were the most common consumed, accounting for 54.6% of total supplements used; performance enhancers comprised 24.7% of total intake; and herbs comprised 20.7% of total supplements used. Dietary supplements were reportedly consumed 5 times or more per week by 34.3% of the participants, 3 to 4 times per week by 27.2% reported consuming, and 1 to 2 times per week by 38.5% of participants.

Table 3 ranks the 10 most commonly consumed dietary supplements, as well as gender differences. Overall, multivitamins, vitamin C, creatine, ephedra, ginseng, and calcium were the most frequently consumed products. Significantly more men than women reported consuming iron, creatine, and ginseng ( $P<0.05$ ).

Reasons for consuming supplements given by those who responded are listed in Table 4. Subjects were allowed to select as many reasons as applied to them for each dietary supplement used. The two most common reasons for consuming supplements were "promote general health" and "performance enhancer." Males were significantly more likely to give the reason "performance enhancer," while females significantly selected "recommended by family or friend" more often ( $P<0.05$ ).

A total of 201 participants (23%) reported consuming a weight loss supplement during the previous 6 months. Forty percent reported a consumption rate of 5 times or more per week, 31% reported 1 to 2 times per week, and 28% reported 3 to 4 times per week. A higher percentage of females (36%) than males (22%) reported consuming weight loss supplements during the previous 6 months, although this was not statistically significant. Forty-three percent of those reported using weight loss supplements reported current use of ephedra. Those who reported using weight loss supplements were significantly more

likely to report consuming at least one other dietary supplement ( $P<0.05$ ).

According to self-reported aerobic exercise practices, over half (53%) of all participants reported performing aerobic exercise 3 to 4 times per week. Thirty-one percent reported 5 times or more per week, 13% reported 1 to 2 times per week, and 4% reported never or rarely. There was no statistical difference in aerobic exercise frequency between supplement and nonsupplement users ( $P<0.05$ ).

According to self-reported anaerobic exercise practices, less than half (47%) reported performing anaerobic exercise 3 to 4 times per week. Twenty-eight percent reported 5 times or more per week, 22% reported 1 to 2 times per week, and 3% reported rarely or never. There was no statistical difference in anaerobic exercise frequency between supplement and non-supplement users ( $P<0.05$ ). Significantly more males reported increased (5 times or more) anaerobic exercise while consuming perceived performance enhancers than those who reported consuming vitamins and minerals or herbals.

Three hundred and fifty-two participant responses were analyzed for sources of information. Participants could select as many sources as applied. Table 5 displays rank order format of the responses. Participants most often listed "other (family or friend)" as a source of information for consuming dietary supplements (53%) followed by magazine (50%), sales store associate (23%), and Internet (18%). Males selected magazines as their source of information significantly more than females. Females selected doctors significantly more than men ( $P<0.05$ ).

A total of 327 participants responded to the question "have you experienced any adverse events while consuming dietary supplements?" Participants could select as many adverse events as applied to them. Two hundred and thirty-one participants

Supplement			Top 10 by gender Males (n=44)			Top 10 by gender Females (n=87)		
	n	%		n	%		n	%
Multivitamin	300	56	Multivitamin	251	57	Multivitamin	49	56
Vitamin C	147	28	Vitamin C	129	29	Vitamin C	18	21
Creatine	122	23	Creatine	120	27	Calcium	17	20
Ephedra	112	21	Ginseng	103	23	Ephedra	16	18
Ginseng	110	21	Ephedra	97	22	Iron	15	17
Calcium	106	20	Calcium	89	20	Prenatal	12	14
Vitamin E	81	15	Vitamin E	72	16	Vitamin A	9	10
Vitamin A	68	13	Garlic	65	15	Vitamin E	9	10
Iron	68	13	Vitamin A	59	13	Ginseng	7	8
Garlic	65	12	Iron	53	12	Vitamin B6	7	8

Table 3. Top 10 Dietary Supplements Consumed (n=531)

Reason Supplement Consumed	n
Promote general health	667
Performance enhancer	475
Prevent illness	145
Did research about it	120
Recommended by family or friend	94
Physician directed	44
Recommended by sales person	15

Note: Participants could choose more than one reason/supplement. Some respondents gave no reason for consuming a supplement.

Table 4. Frequency of Reported Reasons for Consuming a Dietary Supplement

Source	n
Other (friends, family, etc)	185
Magazines	175
Sales Store Associate	81
Internet Sites	63
Doctors	58
Books	55
TV News	55
TV Programs/Commercials	45
Allied health care professional	37
Professional Journals	25
Newspapers	17
Radio	16

Note: Participants could choose more than one source. Some respondents gave no source of information for consuming a supplement.

Table 5. Frequency of Reported Sources of Information for Consuming Dietary Supplements

reported no adverse events, and 96 (29%) reported one or more adverse events. A total of 139 adverse event selections were made (Table 6). Of those reporting adverse events, palpitations (46%) were experienced most frequently followed by dizziness or confusion (30%), tremors (26%), abdominal pain (24%), numbness or tingling of arms or legs (16%), and loss of consciousness (4%). Females experienced significantly more palpitations, tremors, and dizziness or confusion than males ( $P<0.05$ ). Accounting for all adverse events reported, no significant difference was found between males or females.

One hundred and thirteen participants in this study reported consuming ephedra. A total of 52 adverse events (46%) were reported specifically by participants (n=113) consuming ephedra. Approximately 17% reported experiencing palpitations, while not quite 10% reported experiencing tremors.

Of those reporting consuming creatine, 11% reported experiencing palpitations, while 8% reported abdominal pain. In addition, 19% of the participants consuming androstenedione reported experiencing palpitations.

Three hundred and forty-five participants specified establishments where they routinely purchase dietary supplements. Participants could select as many establishments as applied. Sixty-four percent reported purchasing dietary supplements from a nutrition store, 33% from the commissary or Post Exchange (PX) store, 27% from a health food store, 20% civilian establishment, and 9% from mail order or Internet. No statistical difference between males and females and reported establishments for purchasing dietary supplements (Table 7).

Adverse event	n	males	females
Palpitations	46 (46%)	30	14
Dizziness or Confusion	29 (30%)	19	10
Tremors	24 (25%)	17	7
Abdominal pain	23 (24%)	18	5
Numbness or tingling of arms or legs	15 (16%)	13	2
Loss of consciousness	4 (4%)	4	0
Not experiencing adverse events	231	198	33

Note: Participants could choose more than one adverse event/supplement. Some participants gave no response.

Table 6. Frequency of Soldiers Consuming Dietary Supplements Reporting Experiencing Adverse Events (n=327)

	n
Nutrition Stores	221
Commissary/Post Exchange	114
Health Food Stores	92
Civilian Establishment	70
Mail Order/Internet	32

Note: Participants could choose more than one establishment/supplement. Some respondents did not report where dietary supplement(s) was/were purchased.

Table 7. Frequency of Soldiers Reporting Establishments for Purchasing Dietary Supplements (n=345)

## Discussion

Controlled randomized trials and observational studies are providing information about potential positive and negative effects of vitamin and mineral dietary supplements. On the positive side, there is evidence that folic acid consumed by women in the preconception period reduces the occurrence of neural tube defects in babies.<sup>19</sup> Folic acid also decreases the risk of cardiovascular disease.<sup>20</sup> Vitamin E may prevent prostate cancer, cardiovascular disease, and reduce the risk of colon cancer.<sup>21-23</sup> Selenium may prevent various cancers.<sup>24</sup>

Additional studies have shown that there are negative effects associated with consumption of dietary supplements. Beta-carotene appears to increase the risk of lung cancer in individuals who smoke.<sup>25</sup> Excessive intake of vitamin A in early pregnancy increases the risk of congenital malformations in the fetus.<sup>26</sup> Still, there is a general perception that supplements pose little or no health threat to those who consume them.<sup>4</sup>

## Dietary Supplements Sold on Military Installations

Not only is there an increase in the number of dietary

supplements on the market, but they also have become more readily available to military personnel. In 1994, the first General Nutrition Center (GNC) "health" store was awarded an Army and Air Force Exchange System (AAFES) contract and opened for business on a military installation. Presently, there are 92 GNC stores located worldwide on Air Force, Army, Marine, and Naval installations. In 2001, the total sales in GNC stores on military installations were 31 million dollars. While these stores may contribute only a small portion to the total national sales in this industry, it is a substantial amount considering the limited population it serves. Furthermore, by the very nature of the store being located on the military installations, it may inappropriately appear that the military is promoting use of these supplements.

The majority of Soldiers who reported purchasing dietary supplements purchased them from a nutrition store (64%), and the Commissary and PX (33%). While the GNC by name was not specified as a selection on the questionnaire, it could be assumed that Soldiers interpreted the nutrition store as the GNC store available in the military shopping complex. In addition, the top 10 dietary supplements sold by GNC in 2001 closely matched consumption patterns of the Soldiers in this study.<sup>27</sup>

## Usage of Dietary Supplements in the Study Population

Supplement use in this study population is higher than reported for the U.S. population. The majority (60.9%) surveyed consumed vitamin and mineral, performance enhancing, or herbal dietary supplements. Results of this study are consistent with consumption rate and types consumed reported in Special Forces and Ranger candidates, with multiple vitamins and vitamin C supplements the two most commonly consumed dietary supplements.<sup>12</sup> It appears that creatine has slightly increased in popularity and consumption between their study time frame and the current study (18% to 23%). A notable percentage (21%) of this population is consuming ephedra.

## Reasons for Consuming Supplements

Studies indicate that individuals cite a variety of reasons for consuming dietary supplements. Reasons include a desire for increased energy, enhanced athletic performance, strength, vitality, and prevention of illness.<sup>9</sup> Other reasons cited include improving overall nutrition status, decreasing susceptibility to or severity of disease, preventing fatigue, and enhancing personal appearance.<sup>6</sup> In addition, aggressive marketing of supplements, positive reviews in the lay literature, and dissatisfaction with the perceived impersonal approach of Western medicine have all been touted as reasons why patients seek herbal medicine and other supplements.<sup>28</sup>

Of those who had an opinion, the majority of this population selected "promote general health" (n=667) followed

by "performance enhancer" (n=475) as the reason to use supplements.

### Sources of Information for Dietary Supplements

The FDA recommends that individuals consult a physician or other health care professional (for example, Registered Dietitian, Registered Pharmacist, Physician Assistant) prior to consuming any dietary supplement.<sup>29</sup> In contrast to the FDA's recommendation, participants were more likely to seek information on dietary supplements from nonmedical and nonscientific sources.

Participants reported learning about supplements from diverse sources (see Table 5). Of those who had an opinion, approximately half selected friend or family member, followed by magazines and sales store associates. The combined frequency that doctors and allied health professionals were selected closely equals the frequency for which sales store associates were selected (84 vs 81). These findings are in agreement with primary sources of information on dietary supplements reported by patients in a family practice clinic and military health club participants with regards to receiving the majority of their information from nonscientific sources.<sup>14,28</sup>

Popular sports magazines and Internet sites are capable of providing accurate scientific-based information concerning dietary supplementation in a nonbiased manner. However, consumers should be aware of possible conflicts of interest in these websites and publications because the information is typically funded by manufacturers of the supplements. In addition, testimonials of individuals with no medical background may be the source of information. On the other hand, health care providers and allied health professional can disseminate findings from well-controlled, peer-reviewed research regarding dietary supplementation.

### Adverse Events

Some inherent risk is present in taking any over-the-counter supplement. Although in most cases this risk is small, published reports describe examples in which harm has occurred, including death in some cases. In this study, a high percentage (18%) of total participants consuming a dietary supplement reported experiencing adverse events, and it appears they continued consumption regardless of their perception of negative adverse events. This result is in contrast to the estimated report of only 1% of adverse events actually reported to the FDA. As mentioned previously, the current reporting system may not be capturing true results of adverse events. Nevertheless, this population appears to be experiencing a significant number of adverse events.

Ephedra and creatine had the highest reported incidence of adverse events in this study. These two dietary supplements are typically marketed for weight loss and performance enhancement. This population could be considered at increased risk of dietary supplement-related adverse events from use. However, within the limits of this study, experienced or reported adverse events could not be attributed specifically to dietary supplement consumption.

### Herbal Preparations and Surgery

Military personnel are currently deployed around the world and these deployments increase the risk of becoming injured and requiring immediate surgery. Research on herbal medicines demonstrates this category of dietary supplements may potentially pose risks for patients undergoing surgery. Morbidity and mortality associated with herbal supplements may be more likely in the perioperative period because of the polypharmacy and physiological alterations that occur.<sup>30</sup>

Eight commonly consumed herbals have been reported to affect perioperative care.<sup>31</sup> Complications include increased risk of a myocardial infarction, stroke, bleeding, hypoglycemia, inadequate oral anticoagulation, tachycardia, hypertension, and prolonged or inadequate anesthesia. Five of the eight herbal dietary supplements noted are being consumed in the current study population: ephedra (21.3%), ginseng (20.7%), garlic (13.6%), ginkgo biloba (9.6%), and echinacea (5.8%). This study recommends that these herbals be discontinued 2 to 3 weeks prior to any surgery. Consumption of these herbs by deployed Soldiers could potentially impact their health if immediate surgery is required.

### Performance Enhancing Products

Athletes appear to be searching for the latest information on dietary supplements in hopes of improving their performance and gaining a competitive edge. Like athletes, the rigorous physical demands placed on Soldiers may also be a motivating factor to consume dietary supplements to enhance physical performance.

The heavy media marketing of nutritional supplements requires close inspection of the interpreted research and the claims that are made. Many claims are unfounded and others have manipulated or distorted the outcome of clinical studies. There is some reliable scientific data supporting such aids as caffeine, creatine, and sodium bicarbonate. However, most purported performance-enhancing supplements have not shown to enhance performance.<sup>32</sup>

## Ephedra

Ephedra is also recognized by names such as ephedrine and ma huang. It is an herb that is a common ingredient in products marketed for weight control, energy augmentation, and respiratory function involvement.<sup>33</sup> Ephedra acts somewhat like an amphetamine, a central nervous stimulant that excites the cardiovascular system. It can elevate blood pressure, increase heart rate, cause palpitations, nervousness, insomnia, headaches, and is associated with thromboembolic phenomena.<sup>34</sup>

An improvement in exercise performance capacity with ephedra is not backed by clinical research studies.<sup>35</sup> However, serious adverse events are associated with this herb. Since 1994, the FDA has received and investigated more than 900 reports of adverse events associated with the use of products containing ephedra. Most events occurred in young to middle-aged, otherwise healthy adults, who were using the products for weight control and increased energy. The American Association of Poison Control Centers suspects ephedra in 81 deaths and dozens of cases of high blood pressure, seizures, strokes, and heart attacks from January 1993 to February 2001.<sup>36</sup> Furthermore, ephedra has been implicated as the cause of death or permanent disability in 23 previously healthy athletes over a 2-year period.<sup>37</sup>

If the recommended dose of ephedra is exceeded through supplement use, as can easily happen with overzealous consumers, the results may be serious, if not fatal. With 21% of dietary supplement users in this study reporting consuming ephedra, and 46% of those self-reporting an adverse event, it is important for health care providers to alert Soldiers to the physical risks of consuming ephedra supplements and the importance of recognizing and reporting adverse events to the proper authorities.

## Creatine

Creatine is formed by combining the amino acids glycine, arginine, and methionine. It is also produced in physiologic amounts by the liver, kidneys, and pancreas.<sup>38</sup> In clinical studies, creatine has been found to increase high-intensity intermittent exercise capacity in humans.<sup>39</sup> Over the last few years, creatine has increased in availability and use, particularly in men's sports. However, information regarding long-term and high dose use is limited, and use in combination with other supplements remains unknown.<sup>14</sup>

In clinical studies of individuals consuming creatine, some of the observed adverse events include muscle cramping, dehydration, gastrointestinal distress, nausea, and seizures.<sup>40</sup> A significant number of participants in this study population consuming creatine (19%) self-reported adverse events.

Abdominal pain and palpitations were most frequently reported. Creatine's other observed adverse events were not specifically questioned in this study, but these should be addressed in future research.

## Iron

Athletes in endurance sports, especially running sports, may have a higher dietary iron requirement than nonathletes. A negligible amount of iron is lost in urine and sweat, but runners have increased iron loss in the gastrointestinal tract.<sup>41</sup> No evidence indicates that ingestion of iron is performance enhancing or ergogenic. However, high serum iron may contribute to the pathogenesis of atherosclerosis.<sup>10</sup> Excess iron intake may be associated with cardiovascular disease and cancer.<sup>42,43</sup>

An unexpected finding of this study was the high percentage of males consuming iron supplements (12%). Forty three percent of males reported consuming iron supplements for general health, while 13% reported consuming iron as a performance enhancer. Thus, study participants may be at increased risk of iron overload due to dietary supplement consumption.

## Weight Loss Supplements

The number of participants who reported consuming weight loss supplements (23%) in the previous 6 months is a concern in this population. Military weight requirements may influence consumption of dietary supplements advertised as weight loss aids, and influence Soldiers to consume them if they perceive themselves close to exceeding their maximum weight allowance for height. Many products touted for weight loss contain ephedra.

## Limitations and Strengths of the Study

It is important to note this study's limitations. A potential source of error in assessing dietary supplement intake derives from participant misperception or misunderstanding. Supplement use in the current study involved self-reporting. Therefore, misreporting (underreporting or overreporting) along with misinterpretation of questions (either intentional or unintentional) is possible. Additionally, participants were all active duty Army enlisted Soldiers. Caution must therefore be used before generalizing the results to a broader population.

The questionnaire for data collection use presented many difficulties, and possible measurement limitations. More than 30,000 dietary supplements or preparations are available to consumers, and these formulations change over time. An all-encompassing list of supplements was not feasible. The



questionnaire was designed to list dietary supplements that are commonly consumed in a "pick list," and provide space for participants to write in any additional supplements in an "other" category. In addition, there is no readily accessible and well-maintained database for dietary supplements like that available for foods and prescription drugs.

The strength of this study is the design permitted collection of data from various military units assigned throughout the U.S. Participants were consenting Soldiers obtained from a representative sample of Soldiers. Because this was a randomized population-based sample, it may be quite representative of dietary supplement users among the Army's enlisted active duty population.

### **Further Research**

The findings in this exploratory study provided information about the extent of dietary supplement use in the Army's active duty enlisted population and an indication of reasons Soldiers consume these products. Further research should use a theoretical behavior model that can provide researchers with a greater understanding of factors associated with dietary supplement consumption.

Weight loss supplements appear to be consumed at a level for concern. The current study did not ask about types of supplements consumed specifically for weight loss purposes. Future studies should focus on exploring types and frequency of dietary supplements consumed for weight loss.

Current understanding of the prevalence and patterns of supplement use in the Army active duty population is limited and needs to be enhanced with future research. Furthermore, it is recommended that further studies include a larger sample of females. While this study reports on the largest female sample known to date, data would be enhanced if a larger sample size were studied.

### **Health Care Screening for Dietary Supplements**

The Army Surgeon General established in May 2000, that all military health care beneficiaries would be screened for dietary supplement use during medical visits. Research shows that a high percentage of people do not inform their physician of their use of alternative medical therapies, including dietary supplements.<sup>4</sup>

According to one study, approximately 25% of Americans who consult their physician about a serious health problem are employing unconventional treatments, such as herbal or homeopathic therapy, but only 70% of these patients inform their physician of such use.<sup>44</sup> Use of dietary supplements

and nonprescription medications as reported on a written medical questionnaire was compared with use reported during a structured interview.<sup>45</sup> Prevalence of use on the written self-report was 30.5% compared with 61.0% reported during a structured interview. A survey of 200 patients attending a family practice clinic reported only two thirds of the patients stated that they had informed their physician about the use of supplements.<sup>18</sup> With this information of past studies, it is important for health care providers to specifically elicit and document a history of dietary supplement use.

It is not clear why dietary supplement products appear to be popular among Soldiers. Perhaps Soldiers have a higher level of exposure and vulnerability to dietary supplement marketing efforts on television, the Internet, and in popular magazines that target healthy and athletic individuals. It could also be speculated that because Soldiers are typically in good health, they are more likely to self-medicate with dietary supplements than to rely on more traditional pharmaceuticals. Perhaps Soldiers are seeking to enhance body image, lose weight, or improve their athletic performance for the physical fitness test. Free medical care is provided to all military personnel, making it unlikely that a lack of access to medical practitioners contributes to supplement use. Clearly, future studies should seek to find why consuming supplements is popular in this seemingly healthy population.

### **Routine Assessment of Dietary Supplement Intake**

Given the frequency with which Soldiers in this study reported consuming dietary supplements, there will be increasing demand for health care providers to provide Soldiers with evidence-based advice about these products. Assessment should include which supplements they are consuming, why they are using dietary supplements, frequency, and what doses they are consuming. Health care providers also need to be cognizant of the adverse effects of these products, their potential toxicities, and the possibility of deleterious drug interactions. Additionally, they need to assess the possibility of harmful interactions between dietary products and prescribed or over-the-counter medications, and must be alert to the manifestations of those interactions in their patients. Furthermore, health care providers should faithfully report any known or suspected problems to the FDA Med Watch by calling 1-800-FDA-1088.

### **Education Needs for the Active Duty Population**

Results of this study reveal that the majority of Soldiers are consuming dietary supplements, receive most of their information about dietary supplements from nonscientific sources, and have a high percentage of self-reported adverse events. These data substantiate the need for continued education programs directed to enlisted Soldiers at the unit level by health

care providers. Targeted educational programs on the appropriate use of dietary supplements and their known beneficial and potential harmful effects could benefit Soldiers. Studies have found that individuals with greater nutrition knowledge were less likely to capriciously include supplements in their diet.<sup>11</sup> While many studies indicate benefits of some vitamin and mineral supplements, the benefits of other dietary supplements are dubious, and consequences of their long-term use for the most part are unknown. Education focused on providing Soldiers with current, scientific information on dietary supplements would afford them the opportunity to make informed decisions concerning their dietary supplement intake, and potentially improve their health status.

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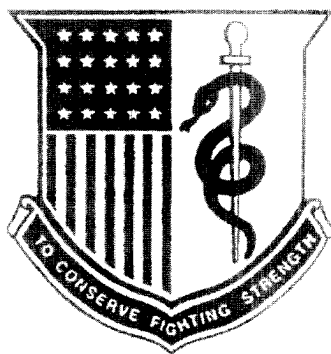
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